BRIEF REPORT

Rising Oseltamivir Use Among Hospitalized Children in a Postpandemic Era

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ABSTRACT

BACKGROUND: Oseltamivir prescribing among pediatric inpatients with influenza varied from 2% to 48% prior to the 2009 H1N1 pandemic. After the pandemic, prescribing guidelines were expanded, and studies reported benefits for hospitalized children. Post-pandemic prescribing practices among children are unclear.

OBJECTIVES: To report the rate of oseltamivir use and to identify factors associated with its use among inpatients with confirmed influenza infection from 2010 to 2014 at a tertiary children's hospital.

METHODS: We conducted a retrospective cohort study of inpatients with polymerase chain reaction–confirmed influenza from December 2010 to April 2014 at Children's Hospital Colorado. The primary outcome was oseltamivir use. Variables regarding demographics, underlying medical conditions, diagnoses, and hospital course were also explored. Univariate and multivariate logistic regression analyses were performed.

RESULTS: Among 395 inpatients with influenza, 323 (82%) received oseltamivir. In univariate analyses, oseltamivir use was associated with admission within 48 hours of symptom onset (89% vs 77%), ICU admission (88% vs 79%), longer length of stay (90% for >6 days vs 77% for ≤2 days), and influenza A H1N1 infection ($P < .05$ for all). In multivariate logistic regression analysis, longer length of stay, illness during the 2013–2014 season, and admission within 48 hours of symptom onset were associated with higher odds of oseltamivir use.

CONCLUSIONS: Oseltamivir use for children with influenza in the postpandemic era is increasing at our institution, aligning with official recommendations and reported benefits. We report highest use for patients in the 2013–2014 season, those who present early in their illness, and those requiring a prolonged hospital stay.

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Oseltamivir is an oral antiviral medication approved by the US Food and Drug Administration (FDA) for the treatment of influenza infection and the prevention of its complications. The American Academy of Pediatrics (AAP) provides updated guidelines annually regarding the appropriate use of oseltamivir to treat influenza infection in children. Before the 2009 influenza A H1N1 pandemic, oseltamivir was FDA-approved and AAP-endorsed for the treatment of acute influenza infection in patients older than 1 year of age with symptom onset of <48 hours.[1,2]

During this prepandemic era, several studies estimated oseltamivir prescribing rates among hospitalized children with influenza infection, with a high proportion of these patients being critically ill. One single-institution retrospective study from 2000 to 2005 reported a prescribing rate of 16.1% among 305 eligible inpatients with laboratory-confirmed influenza who met the initial FDA prescribing criteria.[3] Another review of laboratory-confirmed influenza hospitalizations among children in 9 states from 2003 to 2004 reported oseltamivir treatment rates from 3% to 34%, depending on geographic location.[4] Other studies of inpatients with influenza from 2003 to 2009 suggested that as few as 2% of pediatric inpatients received oseltamivir[5] or that prescribing increased to 48% by 2008.[6] Thus, there is significant variation in reported prescribing in the prepandemic era.

During the 2009 pandemic year, the FDA authorized emergency use of oseltamivir for the treatment of children <1 year of age[7,8] with published pandemic prescribing rates as high as 77% to 90%.[9,10] After 2009, the FDA expanded prescribing guidelines to include neonates,[11] and a growing body of literature emerged reporting benefits of oseltamivir for hospitalized children.[9,12–16] Conversely, literature also emerged contesting the efficacy of oseltamivir, failing to find benefit in comprehensive meta-analyses of published and unpublished work,[17] raising concerns of reporting bias in industry-funded oseltamivir trials and potential methodological flaws.[18,19] Thus, in the context of evolving prescribing guidelines and conflicting bodies of literature, oseltamivir prescribing patterns have likely changed. Yet, to our knowledge, a long-term study of oseltamivir prescribing among inpatient children with influenza infection in the postpandemic era has not yet been reported.

In addition, exploring patterns of oseltamivir use can provide insight into the extent to which physicians follow new recommendations regarding influenza treatment, contribute to the understanding of oseltamivir use in hospitalized children, and identify whether certain patient-related factors, such as sociodemographic characteristics or risk groups, influence prescribing.

The primary objective of this study was to report oseltamivir use among pediatric inpatients with laboratory-confirmed influenza infection at a tertiary children's hospital during the postpandemic period (2010–2014). Our secondary objective was to identify factors associated with oseltamivir use.

METHODS

Study Setting and Population

The study was performed at Children's Hospital Colorado (CHCO), an academic tertiary care center serving the Denver metro area (population of ~2.5 million people), greater Colorado, and surrounding states. In addition to the main campus (~500 beds), CHCO provides inpatient care at 6 satellite locations, with an additional 135 beds, with ~18 000 inpatient admissions per year. To create the study cohort, a computer database queried electronic medical records (EMR) hosted by EPIC (Verona, WI) to identify children hospitalized with laboratory-confirmed influenza infection. Patients were included in this study if they were hospitalized at CHCO (Aurora, CO) or an affiliated site with confirmed influenza infection during the 4 postpandemic seasons starting December 1, 2010, and ending April 12, 2014. Repeat hospitalizations were excluded if hospitalization followed a previous stay within 30 days for confirmed influenza infection. This study was approved by the Colorado Multiple Institutional Review Board.

Design

This retrospective cohort study used data regarding demographics, symptoms, high-risk medical conditions,[20] admission diagnoses, viral subtype, oseltamivir treatment, and hospital course abstracted from the EMR. Data were managed with REDCap (Research Electronic Data Capture) tools hosted at the University of Colorado.[21]

Respiratory specimens were tested by either Direct Fluorescent Antibody, influenza A and B polymerase chain reaction (Genexpert, Sunnyvale, CA), xTag Respiratory Virus Panel (Luminex Molecular Diagnostics, Toronto, Canada), or Film Array (Salt Lake City, UT). Influenza subtypes included H1N1, H3, A (not otherwise specified), and B.

Definitions

Oseltamivir use was the primary outcome and was defined as EMR-recorded receipt of oseltamivir during hospitalization. An underlying medical condition was defined as any condition considered high risk for influenza related complications and included underlying chronic pulmonary conditions (including asthma), hemodynamically significant cardiac disease, immunosuppressive disorders or therapy, chronic renal dysfunction, metabolic disease, neurologic disorders compromising respiratory function, and long-term aspirin therapy.[20] Hypoxia was defined by use of supplemental oxygen during hospitalization. Immunosuppression included patients with any primary immunologic dysfunction, disorders of malignancy, transplantation, HIV, or current receipt of immunosuppressive agents noted in the hospital encounter. PICU admission was considered at any time during the hospitalization. Ventilator dependence was defined as intubation during hospitalization.

Analysis

Descriptive statistics were performed to determine the proportion of patients receiving oseltamivir throughout the study, by influenza season, and by age group. Univariate analyses identified individual factors predictive of oseltamivir use with

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χ^2 analyses or Fisher's exact test for proportions and Wilcoxon rank-sum tests for non-normally distributed variables. To select independent predictors of oseltamivir use, multiple logistic regression analysis with a backward elimination selection procedure was applied. Parameters trending toward statistical significance ($P < .25$) by univariate analysis were included, and predictors with the highest P value were removed from the model 1 at a time until achievement of the best model fit. P values were interpreted at a .05 level of significance. Data were analyzed using SPSS 22 (Chicago, IL) and SAS 9.3 (Cary, NC).

RESULTS

From December 1, 2010, to April 12, 2014, there were 389 patients representing 401 hospitalizations, with 395 inpatients meeting inclusion criteria, with a median age of 48 months (interquartile range [IQR] 16–98 months); 323 (82%) received oseltamivir. Patients experienced a median duration of 3 days of preceding symptoms (IQR 1–6 days) before admission. Figure 1 displays the proportion of patients receiving oseltamivir by study year and location. During the 2011–2012 influenza season, a statistically significant difference in prescribing existed between the PICU and wards (76% vs 37%; $P = .009$); there were no differences for other prescribing years. Figure 2 depicts oseltamivir prescribing by age group during the study period. A trend toward increased prescribing in patients <3 months of age was not statistically significant.

In univariate analyses, oseltamivir use was associated with admission within 48 hours of symptom onset (89% vs 77%), ICU admission (88% vs 79%), longer length of stay (90% for > 6 days vs 77% for ≤2 days), and infection with influenza A H1N1 and was dependent on admission location ($P < .05$ for all; Tables 1 and 2). In multivariate logistic regression analysis, longer length of stay, illness during the 2013–2014 influenza season, and admission within 48 hours of symptom onset were associated with higher odds of oseltamivir use (Table 3). Changes in oseltamivir treatment recommendations from 2004–2014 are summarized in Table 4.

DISCUSSION

We report high oseltamivir use among pediatric inpatients for the treatment of influenza in 4 postpandemic influenza seasons at our institution. Oseltamivir use increased during the study period, with highest use during the 2013–2014 season. In adjusted analyses, oseltamivir use was associated with longer length of stay, likely representing patients with more severe illness (specific measures of illness severity were not evaluated) and admission within 48 hours of symptom onset. These findings align with newer recommendations after the pandemic year and with published data indicating greater benefit with earlier treatment.[11,16]

Our data revealed that oseltamivir prescribing increased overall during our study period, reaching a high of 97% during the 2013–2014 season. While we did observe a decrease in prescribing during the 2011–2012 season, this was notably a less severe influenza season, which may have influenced physician practice. Our prescribing trends differ from other data in the literature which report a decrease in use after the 2009 pandemic season.[9,10] However, these data only spanned the 1 season after the 2009 pandemic. Oseltamivir prescribing during the 2013–2014 year was even higher than the pandemic year at our institution, which was reported previously

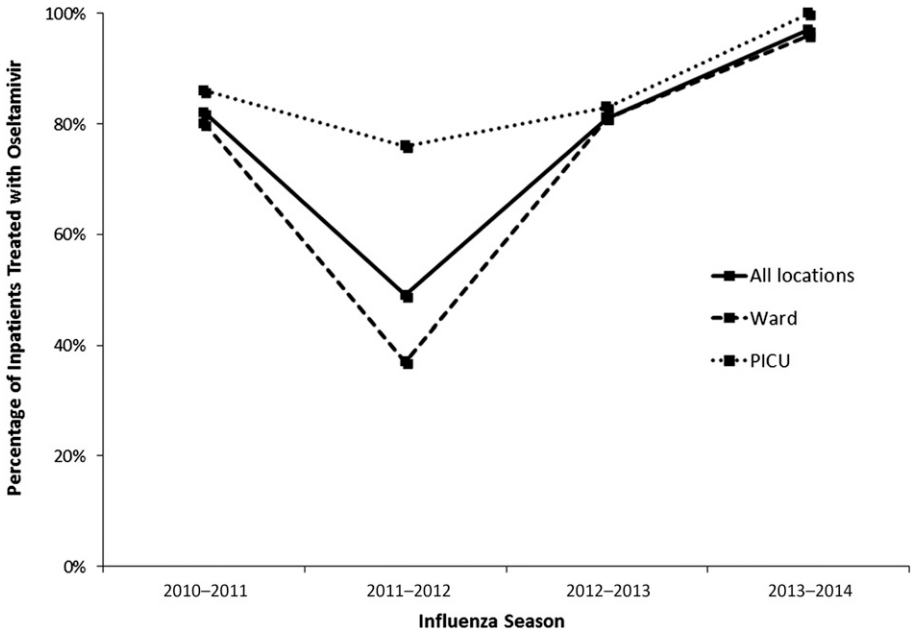

FIGURE 1 Proportion of oseltamivir use among inpatients at CHCO from 2010 to 2014 by patient location.

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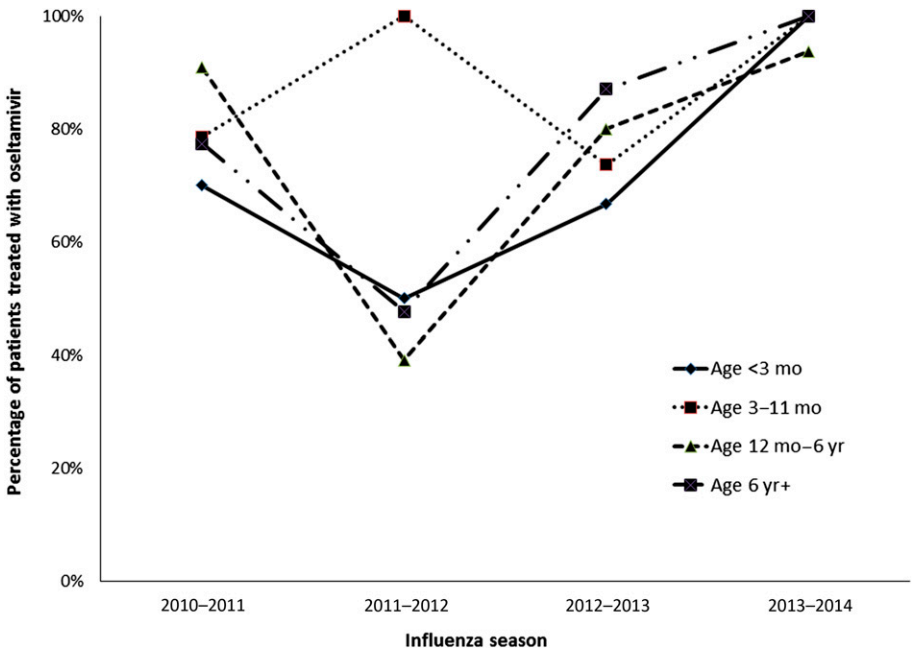

FIGURE 2 Proportion of oseltamivir prescribed for inpatients at CHCO from 2010 to 2014 stratified by patient age.

to be 87% among patients with influenza A H1N1 infection.[8]

The reasons for the increase in prescribing observed in our study are likely multifactorial. First, there have been multiple changes in FDA and AAP recommendations for oseltamivir use among children with influenza infection over the past decade, summarized in Table 4.[1,2,8,11,22,23] With 1 exception, each update has liberalized oseltamivir use, such that most hospitalized children of any age with confirmed or suspected influenza infection are eligible to receive antiviral therapy, regardless of underlying conditions. This may explain the lack of association between oseltamivir use and underlying medical conditions or admission diagnoses noted in our study.

Secondly, oseltamivir use also may be increasing as more studies emerge describing the benefits for hospitalized children. Early neuraminidase inhibitor use in hospitalized children has been associated with a decreased length of hospital stay[12] and decreased likelihood of ICU admission and need for mechanical ventilation.[13,14] Other observational studies have suggested that treatment may improve survival.[19,15,16] However, one must take into account the limitations of retrospective, nonrandomized data, which accounts for much of the published work in the postpandemic era, as well as potential bias from industry-sponsored studies.[18,19] A recent Cochrane review of >100 clinical studies, including previously unpublished data, reported that oseltamivir therapy did not affect hospitalization and did not reduce serious influenza complications like pneumonia, although the authors reported that methodologic differences between the

TABLE 1 Comparison of Patient Characteristics by Oseltamivier Receipt Among Patients with Influenza Admitted to CHCO, 2010–2014

	Total Patients, $n = 389$	Received Oseltamivir, $n = 319$	Did Not Receive Oseltamivir, $n = 70$	P[a]
Demographics				
Age, mo (median, IQR)	54 (16–104)	53 (18–109)	54 (14–95)	.32[b]
Gender (male)	223 (57)	188 (59)	35 (50)	.17
Asthma	70 (18)	61 (19)	9 (13)	.22[b]
Chronic pulmonary disease (excluding asthma)	52 (13)	41 (13)	11 (16)	.52
Global developmental delay	24 (6)	21 (7)	3 (4)	.59[b]
Immunosuppression	23 (6)	19 (6)	4 (6)	1.0[b]
Neuromuscular disorder	24 (6)	23 (7)	1 (1)	.10[b]
No underlying medical conditions	95 (24)	74 (23)	21 (30)	.23

[a] χ^2 test unless otherwise specified with Bonferroni adjustment for multiple comparisons.
[b] Fisher's exact test.

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TABLE 2 Presentation and Hospital Course of Patients by Oseltamivir Receipt Among Patients With Influenza Admitted to CHCO, 2010–2014

	Total Hospitalizations, $n = 395$	Received Oseltamivir, $n = 323$	Did Not Receive Oseltamivir, $n = 72$	P[a]
Presentation or clinical diagnosis				
Respiratory distress	100 (25)	89 (22)	11 (15)	.04
Asthma exacerbation	30 (8)	26 (8)	4 (6)	1.0[b]
Bronchiolitis	13 (3)	9 (3)	4 (5)	.27[b]
Pneumonia	26 (7)	37 (11)	5 (7)	.30[b]
Croup	9 (2)	7 (2)	2 (3)	.67[b]
Acute otitis media	16 (4)	12 (4)	4 (6)	.51[b]
Sepsis	16 (4)	12 (4)	4 (6)	1.0[b]
Influenza season				
2010–2011	88 (22)	72 (22)	16 (22)	<.0001
2011–2012	55 (14)	27 (8)	28 (39)	
2012–2013	134 (34)	109 (34)	25 (35)	
2013–2014	118 (30)	115 (36)	3 (4)	
Influenza strain				
Influenza A unknown	81 (21)	67 (21)	14 (20)	1.0
Influenza A H1N1	119 (30)	116 (36)	3 (4)	<.0001[b]
Influenza A H3	86 (22)	55 (17)	31 (43)	<.0001
Influenza B	110 (28)	86 (27)	24 (33)	.10
Hospital course				
Admission location				
Specialty ward	134 (34)	109 (34)	25 (35)	.023
General ward	225 (57)	191 (59)	34 (48)	
Satellite ward	33 (8)	22 (7)	11 (16)	
Other	1 (0.3)	0 (0)	1 (1.4)	
Length of stay, d, median (IQR)	3 (2–6)	3 (2–6)	2 (2–4)	.13[c]
Day of illness at presentation, median (IQR)	3 (1–6)	3 (1–5)	4 (2–6)	.08[c]
Received antibiotics	245 (62)	202 (62)	43 (60)	.76
PICU admission	135 (34)	119 (37)	16 (22)	.04
PICU length of stay, d, median (IQR)	2 (1–6)	2 (1–7)	2 (1–3)	.48[c]
Ventilator dependence	46 (12)	40 (12)	6 (8)	.30[b]
Intubated or noninvasive positive pressure ventilation	83 (21)	75 (23)	8 (11)	.04[b]

[a] χ^2 test unless otherwise specified with Bonferroni adjustment for multiple comparisons.
[b] Fisher's exact test.
[c] Wilcoxon rank-sum test.

various studies precluded confidence in the results.[17] It will be interesting to note whether these findings will affect oseltamivir prescribing over the subsequent years.

Reasons for high postpandemic oseltamivir use at our institution may include higher illness acuity of patients admitted to a tertiary referral center, institutional guidelines recommending use among hospitalized patients, or a culture of higher antiviral prescribing among physicians and other medical staff. Our univariate analysis demonstrated that a lower proportion of patients admitted to satellite hospitals received oseltamivir, but this is confounded by the lower patient acuity generally seen at these sites. In addition to practice site and performance of rapid testing, physician beliefs about morbidity and mortality benefits have been shown to influence prescribing.[24] Factors influencing antiviral prescribing among providers in the postpandemic era warrant further study.

Our multivariate analysis explored patient-related factors that could influence oseltamivir prescribing and showed that patient age was not associated with oseltamivir use in this study. Although there was a trend to increased use over time for children <3 months, these findings were not statistically significant. This may have been due to a small sample size among this group. This increased trend coincides with the FDA expansion of prescribing guidelines to include children as young as 2 weeks of age in December 2012, and the 2013–2014 AAP recommendations for control and treatment of influenza note that oseltamivir can be used

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TABLE 3 Multivariate Logistic Regression Results With Model Predictor and Odds Ratios, Demonstrating Factors Associated With Oseltamivir Use at CHCO From 2010 to 2014

Model Predictor	Odds Ratio (95% CI)
Duration of illness before admission, ≤2 d vs >2 d	4.91 (2.34–10.29)
Length of stay	
>6 d vs ≤2 d	6.13 (2.36–15.89)
3–5 d vs ≤2 d	1.8 (0.90–3.61)
Influenza season	
2013–2014 vs 2010–2011	9.80 (2.61–36.77)
2012–2013 vs 2010–2011	1.52 (0.68–3.40)
2011–2012 vs 2010–2011	0.17 (0.07–0.40)

Variables with $P \leq .25$ in the univariate analyses were included in the model. Variables included for analysis were gender, age (continuous), days of illness, asthma, neuromuscular condition, hypoxia, length of stay (categorical), PICU admission, PICU length of stay, influenza subtype, respiratory distress, fever, and influenza season.

to treat influenza in both term and preterm infants from birth.[22] Given the impact of influenza on young children,[25] and lack of protection available from immunization for children <6 months of age, the age expansion has important implications regarding the potential to decrease morbidity and mortality in this age group.

There are limitations to this study. The retrospective nature of the study may have introduced misclassification bias as the investigators reviewed other providers' charting to abstract clinically relevant information. In addition to a small sample size, the higher proportion of patients receiving oseltamivir compared with those who did not receive this agent may have introduced further bias. This study did not assess clinical decision-making processes regarding treatment with oseltamivir. Given the variation in oseltamivir prescribing noted by geographic area in previous work,[4] it is difficult to assess the generalizability of our findings to other institutions. Finally, dosing, timing, and duration of therapy were not measured once the patient was discharged from hospital, or before hospitalization.

TABLE 4 Summary of Oseltamivir Treatment Recommendations From 2004 to 2014 by Organization and Year

Year	Organization	Oseltamivir Recommendation or Approval
2007	FDA	Treat children >1 y of age with <48 h symptoms.
2007	AAP	Treat influenza infection of any severity in children at high risk regardless of immunization status.
		Treat any otherwise healthy child with moderate to severe influenza infection who may benefit from a decrease in duration of clinical symptoms.
		Oseltamivir not approved for therapy in children <1 y of age, but 2 studies in younger children did not find drug-attributable toxicities to date.
2009	FDA	Emergency use authorization during H1N1 pandemic approves oseltamivir use for patients <1 y of age.
		Approves oseltamivir use in children with >2 d of symptoms.
		Approval expires June 23, 2010, at which time previous FDA recommendations resume.
2010	AAP	Treat children >12 mo of age at high risk of complications or those hospitalized with presumed influenza.
		Treatment appropriate in patients 3–12 mo of age if providers believe it is indicated.
		Treatment not recommended in children <3 mo of age unless situation critical.
2012	FDA	Treatment approved for children >2 wk of age with symptoms for <48 h.
2013	AAP	Treatment recommended for hospitalized term and preterm infants from birth.

In conclusion, our study demonstrated that oseltamivir use is increasing in a postpandemic era at our institution, with >80% of hospitalized patients receiving therapy in a 4-year period. These increasing prescribing trends align with pediatric governing body recommendations and are of interest in the setting of conflicting evidence in the literature regarding its morbidity and mortality benefits.

Ultimately, our findings provide insight into oseltamivir prescribing practices for hospitalized children in both the ICU and non-ICU settings, as well as the impact of national guidelines in influencing physician practice changes. Our findings suggest that among a multitude of factors that influence prescribing, illness severity and duration of symptoms are leading considerations. Additional studies are needed to confirm these findings in a broader context, to explore factors influencing individual provider prescribing practices, and to further corroborate reported benefits of oseltamivir therapy in hospitalized children, particularly in the non-ICU setting.

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