

Impact of empirical oseltamivir discontinuation in hospitalized patients with community-acquired pneumonia after confirmed negative for influenza

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ABSTRACT

الأهداف: الانفلونزا هو مرض محدد ذاتياً لأغلب الأفراد الصحيين ولكن أحيانا يتسبب هذا المرض بالاضابات او الوفيات. يتسخدم داو أوسيلتاميفير لعلاج داء ذات الرئة المكتسب من المجتمع كعلاج اولي قبل ظهور الفحص النهائي. من المهم ايقاف العلاج عن المريض في حالة ثبوت نتيجة سلبية للفيروس وذلك لتفادي السلبيات الطبية أو المالية التي قد يسببه الاستمرار على العلاج. تهدف الدراسة الى فحص تأثير الوقف المبكر لدواء أوسيلتاميفير للمرضى المنومين في المستشفى نتيجة اشتباه بدء ذات الرئة المكتسب من المجتمع وبعد عينة سلبية للفيروس.

المنهجية: هذي دراسة سريرية بأثر رجعي حيث تم جمع العينات بعد الحصول على الموافقة مجلس المراجعة المؤسسية. تم جمع المتغيرات الديموغرافية (العمر، الجنس، ظهور المرض و مدة أخذ الدواء)، المتغيرات السريرية (مدة المكوث في المستشفى مع إعادة الإسعاف إلى المستشفى).

النتائج: مجموع 210 منوم مشتبه بأصابته بدء ذات الرئة المكتسب من المجتمع تم اندراجهم في الدراسة وقد تم استخدام علاج وسيلتاميفير بشكل أولي معهم وثبت فيما بعد خلوهم من الفيروس. ثلث (33%) من المرضى تم ايقام الدواء عنهم او مايعادل 66 مريض. الباقي من المرضى (69%) تم استكمال الخطة العلاجية لدواء أوسيلتاميفير حتى بعد ثبوت النتيجة السلبية. بعد عزل كل العوامل السريرية وغيرها: ثبت وجود ارتباط احصائي بين تنويم المريض في العناية المركزة مع وقف الدواء المبكر.

الخلاصة: أثبتت هذه الدراسة أن الوقف المبكر لعلاج أوسيلتاميفير للمرضى المنومين في المستشفى نتيجة اشتباه بدء ذات الرئة المكتسب من المجتمع وبعد عينة سلبية للفيروس لا يؤثر سلباً على المريض.

Objectives: To study the effect of appropriate oseltamivir discontinuation in patients hospitalized with pneumonia, after they tested negative for influenza.

Methods: A retrospective study was conducted at King Abdulaziz Medical City, Riyadh, Saudi Arabia. Patients admitted with a diagnosis of community-acquired pneumonia and started on empirical oseltamivir were included. The duration of stay at the hospital and readmission rates were identified. Additionally, we studied factors that led healthcare providers to continue patients on oseltamivir therapy despite testing negative for influenza.

Results: A total of 210 patients were studied. The rate of empirical oseltamivir appropriate discontinuation

was 31% (66 patients). No significant difference was noted between the 2 groups in the length of hospital stay ($p=0.46$). There was no significant difference in terms of 30-day (OR=0.67, 95% CI [0.28-1.59]), 60-day (OR=1.14, 95% CI [0.47, 2.78]), and 90-day readmission rates (OR=1.35, 95% CI [0.35-5.27]). After adjusting for other variables, admission to the intensive care unit was independently associated with appropriate discontinuation compared with patients admitted to general wards.

Conclusions: This study showed that appropriate discontinuation of empirical antiviral therapy is safe, effective, and has no impact on the length of stay and readmission rates.

Keywords: oseltamivir, influenza, community-acquired pneumonia

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Influenza is a respiratory viral infection that presents as a self-limiting disease in most individuals.¹ Globally, the incidence of seasonal influenza is 7%-18%, whereas the incidence of pandemic influenza is estimated to be higher, at approximately 20%-50%.² According to the World Health Organization (WHO), 3-5 million

people are severely ill each year due to influenza.³ Patients at risk of severe complications include the elderly, immunocompromised, and people with chronic conditions, such as pulmonary, cardiac, and metabolic diseases.⁴⁻⁶

Oseltamivir is an antiviral agent belonging to the class of neuraminidase inhibitors and is used to treat and prevent influenza A and B viruses.⁷ Ample evidence exists regarding its effectiveness in treating hospitalized patients suspected of influenza.^{2,7-10} Jefferson et al⁷ found that oseltamivir significantly reduced symptom duration by an average of 16 hour. Moreover, Muthuri et al¹¹ reported a significant reduction in mortality in patients treated with neuraminidase inhibitors during the 2009 influenza A (H1N1pdm09) pandemic.¹¹ Because neuraminidase inhibitors, including oseltamivir, currently represent the most effective option available for treating influenza, ensuring their appropriate use is essential to maintaining their efficacy, as many studies have indicated that inappropriate medication can result in adverse drug reactions, and mortality particularly for elderly patients.¹² More importantly, over-prescription of antimicrobials, including antivirals, can lead to resistance.¹³ In view of these considerations, antimicrobial stewardship programs are designed to ensure appropriate antimicrobial use in local healthcare institutions.^{14,15} One strategy for doing so involves narrowing an empirically broad antimicrobial regimen to specific coverage, depending on diagnostic information.¹⁶

Accordingly, the objectives of this study were to 1) determine the inappropriate use of the empirical antiviral oseltamivir, 2) explore factors likely to lead healthcare providers to continue patients on oseltamivir therapy despite testing negative for influenza, and 3) assess all-cause hospital length of stay and readmission after discharge for both appropriately and inappropriately treated groups.

Methods. A retrospective chart review was conducted at King Abdulaziz Medical City, Riyadh, Saudi Arabia, from January 2016 to December 2018. The study was approved by the Ethics Committee at King Abdullah International Medical Research Center. Data were collected using electronic medical records.

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Confidentiality was ensured by adherence to the World Medical Association Declaration of Helsinki ethical standards.

The study included adult patients (>18 years) admitted to the hospital with a first-time diagnosis of community-acquired pneumonia (CAP) during the study period. All participants had a fever and one respiratory symptom (cough, sore throat, and nasal symptoms), with a multiplex polymerase chain reaction (PCR) panel test for respiratory viruses. Participants were treated empirically. Patients without a documented multiplex PCR panel report and those with confirmed positive influenza A or B infections were excluded.

The pneumonia diagnosis was confirmed by respiratory multiplex panel testing, a reverse transcriptase-PCR. The test was conducted using a nasopharyngeal swab. The testing panel targeted influenza A and B viruses, respiratory syncytial virus A and B, rhinovirus/enterovirus, parainfluenza virus 1-3, adenovirus, human metapneumovirus, and coronavirus OC43 and 229E. The minimal analytical testing time was 4.5 hours, and turnaround times ranged from 6 to 24 hours. The duration of oseltamivir therapy was confirmed from the medication administration record and defined as the total number of days of oseltamivir therapy. The number of additional days a patient continued oseltamivir after a confirmed negative result was calculated separately based on the date of the influenza PCR test result and the date of the last dose of oseltamivir documented in the electronic medical record. The continuation of oseltamivir therapy was considered inappropriate if it was continued beyond 24 hours after the negative PCR multiplex result report date. We chose the 24 hours time frame because it is the acceptable time frame for health care teams to become aware of the result and take appropriate action. The 30-day, 60-day, and 90-day readmission rates were defined as any readmission due to pneumonia within 30, 60, and 90 days of patient discharge. Medical conditions were represented using the Charlson comorbidity index.¹⁷ The final score aggregated the following conditions: diabetes, hypertension, chronic kidney disease, liver disease, pulmonary disease, cardiovascular disease, and cancer. Antibiotic administration was classified as aminoglycosides, vancomycin, colistin, sulfonamides, penicillins, cephalosporins, and carbapenems.

This study aimed to identify factors that led clinicians to inappropriately continue oseltamivir therapy when the results of influenza PCR were negative. The outcome variable was defined as continuing oseltamivir treatment, which could be explained in part by 2 domains: modifying factors and perception variables.

Modifying factors included age, gender, body mass index, and admission year. Perception variables included the type of patient (intensive care unit (ICU) patients or general ward patients), comorbidities, and antibiotic administration.

Statistical analysis. The sample size was determined using the G*Power analysis software. The formula was calculated for z tests, particularly the logistic regression analysis family. The population proportion was acquired from previous literature, and the alpha error was specified at the 0.05 level. Based on these calculations, the minimum required sample size was 200.^{4,18} A purposive sampling technique was used to reach the minimum required number of patients, plus an additional 5% to allow for missing values in the medical records.

The dependent variable (empirical oseltamivir discontinuation) and the independent variables (age, gender, body mass index, admission year, patients in ICU, comorbidities, and antibiotic administration) were all classified into categorical variables. Independent frequency tests were explored using Chi-squared tests, with inferential statistics applied using stepwise logistic regression to test each factor while controlling for other factors. Finally, prediction models were estimated for different readmission rates and length of stay by continued use of empirical oseltamivir therapy, validated through bootstrapping techniques.¹⁹

Results. From January 2016 to December 2018, a sample of 210 patients diagnosed with CAP and started on empirical oseltamivir was included. Half of these patients (51%) were female, and the mean age was 61 years (SD=20). A significant percentage of the patients were diagnosed with hypertension (53%), diabetes (46%), pulmonary diseases (31%), and chronic kidney disease (11%) (**Table 1**). Most patients (69%) continued oseltamivir beyond 24 hours after testing negative for influenza and were classified as inappropriate (late discontinuation). The median duration of oseltamivir therapy was 3 days. Overall, most patients had mild to moderate disease. Only 20% of the patients had severe disease and required ICU admission. When evaluating concurrent bacterial infections, almost all the patients had microbiologic culture specimens obtained during hospitalization (93%). Only 33% of the patients had concurrent confirmed positive bacterial infections (**Table 2**).

There was no significant difference between the late and appropriate discontinuation groups in terms of the frequencies of modifying variables (**Table 3**) and perception variables (**Table 4**), except that a significantly higher percentage of ICU patients were in the appropriate discontinuation group compared to non-ICU patients (52.3% and 26.1% respectively, $p=0.02$). On evaluating the factors associated with the appropriate discontinuation of oseltamivir (**Table 5**) it was found that patients who were admitted to the ICU were more likely to discontinue oseltamivir after testing negative for influenza (OR, 0.3; 95% CI, 0.14-0.64).

Table 1 - Baseline characteristics.

Factor	Empirical oseltamivir discontinuation		
	Appropriate (n=66)	Late (n=144)	Total (n=210)
Percentage of diabetes diagnosis	45.45%	46.53%	46.19%
Percentage of hypertension diagnosis	51.52%	54.86%	53.81%
Percentage of chronic kidney diseases	19.70%	7.64%	11.43%
Percentage of liver disease diagnosis	6.06%	7.69%	7.18%
Percentage of pulmonary disease diagnosis	34.85%	29.86%	31.43%
Percentage of cardiovascular diagnosis	45.45%	34.72%	38.10%
Percentage of cancer diagnosis	10.61%	8.33%	9.05%
Average baseline creatinine clearance	65.08	72.87	70.41
Average length of stay	11.44	11.59	11.54

Table 2 - Associated infection during hospital stay.

Factor	Empirical oseltamivir discontinuation		
	Appropriate (n=66)	Late (n=144)	Total (n=210)
Percentage of concurrent viral infection*	1.52%	6.25%	4.76%
Percentage of bacterial infection	36.36%	29.86%	31.90%
Percentage of bacterial specimens from blood	13.64%	5.56%	8.10%
Percentage of bacterial specimens from sputum	15.15%	15.97%	15.71%
Percentage of bacterial specimens from urine	9.09%	9.72%	9.52%
Percentage of bacterial specimens from cerebral	0.00%	0.69%	0.48%

*viruses include Coronavirus, Adenovirus, Human metapneumovirus, Rhinovirus, and Parainfluenza

Table 3 - Frequency of modifying factors.

Factor	Empirical oseltamivir discontinuation			P-value
	Appropriate (n=66)	Late (n=144)	Total (n=210)	
<i>Age</i>				
>65	34 (32.1)	72 (67.9)	106	0.96
≥65	32 (30.8)	72 (69.2)	104	
<i>Gender</i>				
Male	30 (29.4)	72 (70.6)	104	0.64
Female	36 (33.3)	72 (66.7)	108	
<i>Body mass index</i>				
Underweight	3 (42.9)	4 (57.1)	7	0.17
Normal	15 (23.1)	50 (76.9)	65	
Overweight & obese	48 (34.7)	90 (65.2)	138	
<i>Admission year</i>				
2016-2017	38 (31.4)	83 (68.6)	121	0.99
2018-2019	28 (31.4)	61 (68.5)	89	

Table 4 - Frequency of perception variables.

Factor	Empirical oseltamivir discontinuation			P-value
	Appropriate (n=66)	Late (n=144)	Total (n=210)	
<i>ICU patients</i>				
Non-ICU	44 (26.1)	124 (73.8)	168	0.02
ICU	22 (52.3)	20 (47.6)	42	
<i>Concurrent antibiotic use</i>				
No	5 (38.4)	8 (61.5)	13	0.55
Yes	16 (30.9)	163 (69.0)	197	
<i>Charlson comorbidity index*</i>				
Average score	2.88	2.5	2.61	0.23

ICU: Intensive care unit, *values presented in means

Other factors, such as age, gender, and year of admission were not significantly associated with appropriate discontinuation. The readmission rates were compared between the appropriate and late discontinuation groups (**Table 6**). There was no significant difference between the 2 groups in terms of 30-day (OR=0.67, 95% CI [0.28-1.59]), 60-day (OR=1.14, 95% CI [0.47-2.78]), and 90-day readmission rates (OR= 1.35, 95% CI [0.35-5.27]). Moreover, no significant difference was noted between the 2 groups in terms of the mean length of stay ($p=0.46$).

Discussion. Our objective was to investigate the clinical outcomes associated with the timely discontinuation of oseltamivir, particularly when the

influenza virus was not detected. We hypothesized that knowledge of negative influenza results would lead physicians to discontinue oseltamivir and positively impact patients' clinical outcomes. The study showed that the rate of timely empirical oseltamivir discontinuation among patients admitted with CAP after confirmed negative influenza was suboptimal (31%). The practice of timely de-escalation of antimicrobial therapy, including antivirals, is a critical part of an antimicrobial stewardship program to decrease the emergence of resistance and reduce the overall cost.²⁰ Pettit et al²¹ reported a savings of approximately \$34.16 per patient when the mean time to discontinue oseltamivir was reduced. This cost-saving is expected to be much higher during influenza seasons when the

use of antiviral oseltamivir is anticipated to be higher. Moreover, our study reported no additional benefits in readmission rates and hospital stay duration for patients who continued oseltamivir despite testing negative for influenza. This finding is similar to that of Bohan et al,²² who investigated the outcome of antibiotic de-escalation in patients with healthcare-associated pneumonia and found it to be a safe practice with no impact on the 30-day readmission rate. On the contrary, it was associated with a modest reduction in hospital length of stay.²² Other studies have reported a beneficial effect of de-escalation practice. Tabah et al²³ reported an association between reduction in mortality rates and

de-escalation of antibiotics, particularly in critically ill patients diagnosed with pneumonia. Notably, Bohan et al²² and Tabah et al²³ studied antimicrobial agents in general, whereas our study explored patients empirically treated with oseltamivir.

One of our study observations that warrants further discussion is that ICU patients were more likely to have empirical oseltamivir discontinued after testing negative for influenza, which might be explained by the high level of care provided in this kind of setting. When testing the overall theoretical framework, perception factors had a greater impact on explaining the oseltamivir discontinuation predictive model, which could indicate that clinicians tend to follow guidelines more rigorously when treating patients with worse conditions. This result demonstrates that acute condition management is prone to similar trends highlighted with chronic conditions, where healthcare professionals adhere to guidelines predominantly with patients in worse conditions.²⁴ One explanation for the late discontinuation could be the clinical suspicion of influenza, especially during peak influenza activity in the community, as influenza PCR testing is nearly 50% - 70% sensitive for detecting influenza and approximately greater than 90% specific.^{25,26} However, as observed in our study, extending the antiviral duration after negative results did not result in any further benefit.

Study limitations. Our findings have important implications for antimicrobial stewardship programs. Appropriate oseltamivir discontinuation did not negatively affect patients' clinical outcomes. In contrast, it might carry possible benefits, such as decreasing the emergence of resistance, cost reduction, and appropriate utilization of health care resources. This study's limitations include its retrospective design and its reliance on documented medical records for data collection, including the diagnosis of pneumonia and the length of stay at the ICU, which might have affected our results. Moreover, the oseltamivir discontinuation rate was measured at a single institution, and the results might not apply to other institutions. However, the study adds to the limited literature, shedding light on

Table 5 - Logistic regression model predicting empirical oseltamivir discontinuation.

Odds ratio estimates	Demographics and perception	
	Odds ratio	95% CI
<i>Age</i>		
>65	1.145	0.59 - 2.22
≥65		
<i>Gender</i>		
Male	0.81	0.43 - 1.53
Female		
<i>Body mass index</i>		
Underweight	2.23	0.40 - 13.1
Overweight and obese	1.89	0.90 - 3.97
Normal		
<i>Admission year</i>		
2016-2017	0.88	0.46 - 1.68
2018-2019		
<i>ICU patients*</i>		
Yes	0.30	0.14 - 0.64
No		
<i>Antibiotic use</i>		
No	1.29	0.34 - 4.94
Yes		
Charlson comorbidity	1.16	0.96 - 1.42

*Significant at *p* 0.05. ICU: intensive care unit

Table 6 - Predicting readmission rate and length of stay by continued empirical oseltamivir treatment.

Predictor	30-day readmission	60-day readmission	90-day readmission	Length of stay
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate* (<i>p</i> -value)
Empirical oseltamivir discontinuation	0.67 (0.28 - 1.59)	1.14 (0.47 - 2.78)	1.35 (0.35 - 5.27)	0.75 (0.46)

*presented as mean

an issue that could minimize excess hospitalizations and prevent antimicrobial resistance.

In conclusion, timely discontinuation of antimicrobial therapy, including antiviral therapy, is an essential part of the antimicrobial stewardship program. This study showed that appropriate discontinuation of empirical antiviral therapy in patients with CAP is a safe and effective practice that does not negatively influence the hospital stay duration and readmission rate. Additional efforts may focus on unnecessary antimicrobial therapy optimization strategies. Future studies can focus on other potential benefits, such as cost savings and risk of resistance.

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