ORIGINAL ARTICLE

Appropriateness of antiviral prescribing for influenza in primary care: a retrospective analysis*

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SUMMARY

Background and objective: Antiviral medications cost-effectively reduce influenza-related morbidity and potentially mortality. We sought to assess the appropriateness of antiviral prescribing for influenza.

Method: We performed a retrospective analysis of visits by adults to primary care clinics during influenza seasons from 1 October 2000 to 31 May 2004 with a claims diagnosis of influenza (n = 535) or with an electronic antiviral prescription (n = 25). We defined appropriate antiviral prescribing as the patient having (a) symptoms for 2 or fewer days, (b) fever and (c) any two of headache, sore throat, cough, or myalgias.

Results and discussion: Physicians diagnosed patients with influenza in 102 of 535 (19%) visits with a claims diagnosis of influenza. Physicians prescribed antivirals at 15 of 102 (15%) of these visits. The addition of 25 additional electronic antiviral prescriptions gave a sample of 127 visits and 40 (31%) antiviral prescriptions. Twenty-eight (70%) antiviral prescriptions were appropriate. Among patients who did not receive antivirals, 21 of 87 (24%) met criteria for appropriate antiviral prescribing. Antiviral prescribing was associated with a shorter median symptom duration (2 days vs. 3 days; P < 0.01) and higher median temperature (37.8 °C vs. 36.9 °C; P < 0.01). Physicians prescribed antivirals more frequently to patients who had myalgias (37% vs. 18%; P = 0.04) and an influenza test (67% vs. 28%; P < 0.01). Physicians prescribed antivirals more frequently to Blacks (44%) and patients with other race/ethnicity (67%) than to Whites (20%) or Hispanics (20%; P < 0.0001).

Conclusions: To improve antiviral prescribing for influenza in primary care, interventions need to target the accurate identification of influenza visits, undertreatment, as well as inappropriate treatment.

Keywords: anti-bacterial agents, antiviral agents, drug, drug utilization, influenza, physicians’ practice patterns, prescriptions

INTRODUCTION

Influenza is responsible for up to 226 000 excess hospitalizations and 36 000 deaths per year in the United States and disproportionately affects the elderly (1, 2). The influenza vaccine is the best means of reducing influenza-related morbidity and mortality (3), but its limitations include production problems (1), low vaccination rates (4), and the variable effectiveness of the vaccine itself (5). Given these limitations, there is an important role in management for influenza-specific antiviral medications (6).

Antiviral medications reduce the duration of influenza symptoms by 1–2.5 days (7, 8), reduce complications requiring antibiotics by 30–40% (7–13), may decrease hospitalizations and mortality (14, 15), and are cost-effective (16–20). Despite these apparent benefits, antivirals are rarely used. We previously found that physicians throughout the United States prescribed antivirals to 19% of patients diagnosed with influenza (21).

The appropriateness of antiviral prescribing is unknown. This national rate may represent
appropriate use, inappropriate prescribing, or underprescribing. To be effective, antivirals must be started within 2 days of symptom onset and be used in patients with a high probability of having influenza. In addition, antibiotics continue to be inappropriately prescribed for viral respiratory infections (22). To measure the rate and appropriateness of antiviral and antibiotic prescribing for influenza, we performed a retrospective analysis of visits to the Brigham and Women’s Primary Care Practice-Based Research Network.

METHODS

Setting

The Brigham and Women’s Primary Care (BWPC) Practice-Based Research Network (PBRN) includes nine primary care clinics in the greater-Boston Area. The BWPC Clinics have approximately 95 practicing attending physicians, as well as internal medicine residents who provide longitudinal and urgent care. The BWPC Clinics include two community health-centres, four hospital-based clinics and three community-based clinics. In 2002, the BWPC Clinics provided primary care for over 72 000 adults and children and had over 230 000 patient visits.

Longitudinal Medical Record

The BWPC-PBRN is linked with a common, web-based electronic health record, the Longitudinal Medical Record (LMR). The LMR is the official patient record for the BWPC-PBRN. The LMR is an internally developed, fully functioning electronic record including notes from primary care and subspecialty clinics; International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM)-coded problem lists; medication lists; coded allergies; and lab and radiographic results. In addition, BWPC physicians use the LMR to write prescriptions that can be printed or transmitted to pharmacies electronically. Data regarding new and renewed prescriptions and an archive of prior medications are captured in the LMR.

Data sources

Partners HealthCare, of which Brigham and Women’s is a part, maintains the Research Patient Data Repository (RPDR) which pools inpatient and outpatient encounter data from all Partners HealthCare sites (23). The RPDR identifies claim diagnoses by ICD-9-CM codes and includes information about visit dates, site of care, visit notes and patient demographics, taken from registration information. We linked data derived from the RPDR to data from the LMR, including medication prescribing.

Data extraction and analysis

We identified potential influenza visits to BWPC-PBRN Clinics in two ways. First, we used the RPDR to identify visits with an ICD-9-CM code of influenza (ICD-9-CM 487) made between 1 October and 31 May during the four influenza seasons from the 2000–2001 to the 2003–2004 seasons. Secondly, we used the LMR to identify all prescriptions of the four FDA-approved, anti-influenza medications: amantadine, rimantadine, oseltamivir and zanamivir. We excluded visits by patients aged younger than 18 years old. We excluded visits for which we could find no associated visit note and duplicate notes.

From the note, we extracted the diagnoses as assigned by the treating physician. If the treating physician diagnosed the patient with influenza, ‘flu’, or ‘flu-like illness’ in their note, we collected information about symptoms, vital signs, physical exam findings, and medications prescribed. Because we were interested in antiviral prescribing for acute influenza, we excluded visits at which antivirals were prescribed for multiple sclerosis, Parkinson’s disease, or for influenza prophylaxis. Using these two methods, we identified a cohort of patients with acute influenza who may or may not have received antivirals. We obtained patient demographic information from registration information that is contained within the LMR.

We assessed the appropriateness of antiviral prescribing. In addition, when the physician did not prescribe an antiviral, we assessed if an antiviral prescription would have been appropriate. We defined appropriate antiviral prescribing as the patient having (a) symptoms for 2 or fewer days, (b) fever (patient-reported or temperature ≥38.0°C) and (c) any two of headache, sore throat, cough, or myalgias. Such a definition has a positive predictive of 57–77% in trials of neuraminidase inhibitors when influenza is known to be circulating (7, 24–26).
We also assessed the rate and appropriateness of antibiotic prescribing. We defined an antibiotic prescription as appropriate if there was an antibiotic-appropriate diagnosis mentioned by the treating physician at the acute influenza visit.

Statistical analysis

We used standard descriptive statistics. We used Fisher’s exact test to compare dichotomous variables, the chi-squared test to compare categorical variables and the Wilcoxon rank sum test to compare continuous variables. Because of limited sample size, we did not perform multivariable analyses. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA). P-values <0.05 were considered significant. The Institutional Review Board of Brigham and Women’s Hospital approved the study protocol.

RESULTS

Sample derivation and characteristics

First, we identified 725 visits with a principle or primary billing diagnosis of influenza (Fig. 1). We excluded visits if there was no corresponding note (89), if the note was a duplicate (77), or if a visit was made to the emergency department (24). Of the remaining 535 visits, 102 (19%) had a clinical diagnosis of influenza assigned by the treating physician, 372 (70%) were for non-influenza acute respiratory infections and 61 (11%) were for non-acute respiratory infection diagnoses.

Secondly, we identified 102 visits associated with antiviral prescriptions in the LMR. We excluded visits if there was no corresponding note (10), no reason for the prescription was given (3), the prescription was for influenza prophylaxis (5), or because amantadine was prescribed for multiple sclerosis and Parkinson’s disease (45). Of the remaining 39 visits, 25 had not been identified using claims diagnoses.

The two search methods resulted in a sample of 127 visits for acute influenza: 102 visits identified using billing diagnoses and 25 visits identified using electronic prescribing. Visits from each of nine BWPC clinics were included in the sample. The patients in the sample had a median age of 38 years old, were 76% women, 36% White, 32% Hispanic, 13% Black, and 19% other race and ethnicity (Table 1).

Antiviral prescribing

Antivirals were prescribed at 15 of the 102 (15%) visits identified using claims diagnoses. After adding the 25 acute influenza visits identified using electronic antiviral prescribing, we had a sample in which 40 (31% of 127) patients received antivirals. Antivirals were prescribed at seven different clinics and ranged from three to 10 prescriptions per clinic. Physicians prescribed amantadine in 10 visits, rimantadine in nine visits, oseltamivir in 21 visits and zanamivir in no visits.

Fig. 1. Derivation of the study sample*. *The non-influenza visits were other acute respiratory infections (70%) and non-acute respiratory infection diagnoses (11%). ED, emergency department; MS, multiple sclerosis.

Physicians prescribed antivirals more commonly to Blacks (44%) and other race and ethnicity (67%) than to Whites (20%; \( P < 0.0001 \)) and Hispanics (20%; \( P < 0.04 \); Table 1). Compared with those who did not receive antivirals, patients who received antivirals had a shorter median symptom duration (2 days vs. 3 days; \( P < 0.0001 \)) and higher median temperature (37.8 °C vs. 36.9 °C; \( P = 0.004 \)). Physicians were more likely to prescribe antivirals to patients with myalgias (37%) than patients without myalgias (18%; \( P = 0.04 \)) and to patients who had an influenza test performed (67%) than patients who did not have an influenza test (28%; \( P = 0.01 \)).

Of the 40 antiviral prescriptions, 28 (70%) were appropriate and 12 (30%) were inappropriate (Table 2). Among the 87 visits at which an antiviral was not prescribed, 21 (24%) met criteria for appropriateness. The most common reason for antiviral prescriptions being inappropriate, both for those who did and did not receive antivirals, was symptom duration for longer than 2 days.

### Antibiotic prescribing

Physicians prescribed antibiotics to 13 of 127 patients (10%). No patient received both an antiviral and an antibiotic. Patients who received

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**Table 1.** Influenza visit characteristics and association with antiviral and antibiotic prescribing (\( n = 127^a \))

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sample</th>
<th>Antiviral prescribing (31% overall)</th>
<th>Antibiotic prescribing (10% overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR (^b)</td>
<td>Median</td>
</tr>
<tr>
<td>Age, years</td>
<td>38</td>
<td>28–51</td>
<td>36 vs. 42</td>
</tr>
<tr>
<td>Symptom duration, days (( n = 121 ))</td>
<td>3</td>
<td>2–4</td>
<td>2 vs. 3</td>
</tr>
<tr>
<td>Temperature, °C (( n = 111 ))</td>
<td>37.2</td>
<td>36.6–38.1</td>
<td>37.8 vs. 36.9</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>96</td>
<td>76</td>
<td>30</td>
</tr>
<tr>
<td>Men</td>
<td>31</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>46</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Hispanic</td>
<td>41</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Black</td>
<td>16</td>
<td>13</td>
<td>44</td>
</tr>
<tr>
<td>Other (^c)</td>
<td>24</td>
<td>19</td>
<td>67</td>
</tr>
<tr>
<td>Fever</td>
<td>97</td>
<td>76</td>
<td>35</td>
</tr>
<tr>
<td>Abnormal general appearance (( n = 126 ))</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>45</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>55</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>Cough</td>
<td>101</td>
<td>80</td>
<td>29</td>
</tr>
<tr>
<td>Myalgias</td>
<td>93</td>
<td>73</td>
<td>37</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>26</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Otoscopic abnormality (^d)</td>
<td>9</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>Wheezing</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other lung abnormality</td>
<td>8</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Influenza test</td>
<td>12</td>
<td>9</td>
<td>67</td>
</tr>
<tr>
<td>Blood test, any type</td>
<td>10</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>6</td>
<td>5</td>
<td>33</td>
</tr>
</tbody>
</table>

\(^a\)Except where noted.

\(^b\)IQR is interquartile range.

\(^c\)Race and ethnicity ‘Other’ was not recorded (20), Asian (3), and other (1).

\(^d\)Otoscopic abnormalities included abnormalities of the external auditory canal or the tympanic membrane.
antibiotics had symptoms longer than patients who did not receive antibiotics (median symptom duration, 5 days vs. 2 days; \( P = 0.003 \)). Physicians prescribed antibiotics more commonly to White (20%) and Black (15%) patients than Hispanic (2%) patients or patients with other race and ethnicity (4%; \( P = 0.04 \)).

Among patients receiving antibiotics, nine (69%) did not have a concomitant antibiotic-appropriate diagnosis. At the 114 visits at which antibiotics were not prescribed, one visit had an antibiotic appropriate diagnosis.

### DISCUSSION

In a retrospective analysis of primary care visits, physicians prescribed antivirals to 15% of patients diagnosed with influenza. This agrees with our prior analysis of national data in which physicians prescribed antivirals to 19% of patients diagnosed with influenza (21). In the present study, according to commonly used criteria (7, 24–26), 30% of antiviral prescriptions were inappropriate.

Physicians probably prescribed antivirals inappropriately for a variety of reasons. First, physicians may not be aware of the 2-day limit on prescribing antivirals for influenza. Secondly, physicians may be aware of the 2-day prescribing restriction, but still feel the medications have some benefit. Thirdly, physicians may be fulfilling a desire to ‘do something’ in the form of a prescription medication for patients with a viral illness, similar to findings regarding antibiotic prescribing (27). Finally – and also similar to inappropriate antibiotic prescribing – physicians may be prescribing antivirals to try and maintain patient satisfaction (28–31). For example, as the newer antivirals, oseltamivir and zanamivir, have been directly marketed to patients in the United States, patients may be requesting these medications.

In addition to inappropriately prescribing antivirals, physicians appeared to underprescribe antivirals to patients for whom they appeared appropriate: 24% of patients who did not receive antivirals met the criteria for antiviral prescribing. Possible reasons for underprescribing include physicians’ unfamiliarity with antivirals or physicians’ hesitancy to prescribe medications for what they perceive to be a self-limited illness. In addition, there may be some contraindication to antiviral prescribing that we did not capture in the chart review, though rimantadine, oseltamivir and zanamivir have no important drug–drug interactions.

There were both clinical and non-clinical factors associated with antiviral prescribing. The clinical factors associated with antiviral prescribing were not surprising, such as shorter symptom duration, higher temperatures, more myalgias and more influenza testing. For non-clinical factors, it was surprising to find that physicians prescribed antivirals less frequently to Whites and Hispanics than Blacks and patients with other race and ethnicity. This disagrees with our previous analysis, in which we found that physicians were marginally less likely to prescribe antivirals to non-white patients (odds ratio, 0.4; 95% confidence interval, 0.1–1.0) (21). On reviewing the present data, this finding did not represent a differential distribution of race and ethnicity at clinics with higher antiviral prescribing rates. Our ability to explain this finding is limited by race and ethnicity being collected at the time of patient registration, patients with unknown race and ethnicity, and the small sample size. However, the strength of the association is striking. This finding should be investigated in future studies of antiviral prescribing.

### Table 2. Appropriateness of antiviral prescribing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Received antivirals ( (n = 40) )</th>
<th>Did not receive antivirals ( (n = 87) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration ≤2 days</td>
<td>32 (80)</td>
<td>28 (32)</td>
</tr>
<tr>
<td>Fever Patient reported</td>
<td>34 (85)</td>
<td>68 (78)</td>
</tr>
<tr>
<td>Measured &gt;38°C</td>
<td>16 (40)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Two flu symptoms</td>
<td>36 (90)</td>
<td>72 (83)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (38)</td>
<td>30 (34)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>22 (55)</td>
<td>36 (41)</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (73)</td>
<td>72 (83)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>34 (85)</td>
<td>59 (68)</td>
</tr>
<tr>
<td>Appropriate</td>
<td>28 (70)</td>
<td>21 (24)</td>
</tr>
</tbody>
</table>

*To be considered appropriate, the patient had to have (a) symptoms for 2 or fewer days, (b) fever (patient-reported or temperature >38°C) and (c) any two of headache, sore throat, cough, or myalgias.
The 2-day prescribing restriction is the major barrier to more frequent antiviral use. Even if physicians had prescribed antivirals to all patients who met criteria for appropriateness, only 39% (49 of 127) of patients would have received antivirals. The obvious drawback of interventions to encourage patients to seek care early is that most patients with flu-like illnesses do not have influenza (32). One potential solution lies in the use of electronic health records with shared online patient records that could provide a bidirectional link between the personal and public health systems (33, 34). Such links could assist patients in deciding whether to seek care and, for physicians, could integrate the present influenza prevalence with patient signs and symptoms and assign a probability of a patient having influenza. Such a system could also help clinicians in the event of an epidemic of pathogenic avian influenza (35).

Antibiotic prescribing for acute influenza was even more rare than antiviral prescribing. Physicians prescribed antibiotics to only 10% of patients, less than the 26% we found in our analysis of national data (21). Physicians prescribed antibiotics more to patients who had symptoms longer. In addition, physicians prescribed antibiotics more frequently to Whites and Blacks than to Hispanics or patients with other race and ethnicity. This overall low level of antibiotic prescribing is consistent with other studies that have found decreasing antibiotic prescribing rates for viral illnesses (22, 36).

An important finding from this study is that identifying acute influenza visits was challenging. A billing code for influenza had a positive predictive value for an actual influenza visit of only 19%. Clearly, physicians in our network are using a billing diagnosis of influenza more frequently when they are assigning a clinical diagnosis of another acute respiratory infection rather than for influenza itself. The use of broader initial inclusion criteria, such as an ICD-9-CM code of acute upper respiratory tract infection would probably improve the sensitivity of our search for acute influenza visits, but with greatly reduced specificity. For example, in a preliminary analysis of 185 randomly selected visits with ICD-9-CM codes for acute upper respiratory tract infection and viral syndrome, only 3% mentioned influenza, ‘flu’, or ‘flu-like illness’ as a possible diagnosis.

Identifying antiviral prescriptions was comparatively easier. We identified only a single additional antiviral prescription using claims diagnoses that would not have been identified as an electronic antiviral prescription. Physicians in our network are using the electronic prescribing capability of our electronic health record consistently. We can be confident in future studies of antiviral prescribing that just using electronic prescribing will not miss a significant number of prescriptions.

This study has several limitations that should be considered. First, this study relied on claims diagnoses and electronic prescribing to identify potential influenza visits. As noted above, this strategy had a low positive predictive value. Secondly, this study relied on a retrospective chart review to assess the diagnosis and the signs and symptoms that were included in our definition of appropriateness. A prospective study, though much more costly, could collect data about signs and symptoms systematically and validate the diagnosis of influenza. Thirdly, our definition of appropriateness did not take into account the prevalence of circulating influenza at the time of the visit. As such, our definition of appropriateness was broader and probably more forgiving of physicians than ideal, but this definition of appropriateness performs similarly to or better than other available definitions (9, 37–42). Fourthly, this study had a small sample size, limiting our power to detect differences between groups, precluding our use of multivariable techniques, and preventing the identification of predictors of inappropriate antiviral prescribing.

The influenza vaccine is the best means of preventing influenza-related morbidity and mortality (1). Because of problems with the selection, production and distribution of the annual influenza vaccine, anti-influenza antivirals have a role in therapy, but they are seldom used (21). When used, we found that 30% of antiviral prescriptions were inappropriate. We also found that 24% of those for whom antivirals seemed appropriate did not receive antivirals. In addition, we found that identifying acute influenza visits was challenging. These findings suggest that, to improve antiviral prescribing for influenza in primary care, interventions need to target the accurate, prospective identification of influenza visits, undertreatment, as well as inappropriate treatment.
ACKNOWLEDGEMENTS

This project was supported in part by grant number R03 HS014420 from the Agency for Healthcare Research and Quality. Dr Linder is supported by a Career Development Award (K08 HS014563) from the Agency for Healthcare Research and Quality.

REFERENCES


