Treat ment With Neuraminidase Inhibitors for High-Risk Patients With Influenza: Why Is Adherence to Antiviral Treatment Recommendations So Low?

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(See the major article by Biggerstaff et al on pages 535–44.)

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Annual influenza epidemics result in an estimated 225,000 hospitalizations and between 3300 and 49,000 deaths each year in the United States [1–3]. Individuals such as the elderly, children less than 2 years of age, pregnant women, and those with underlying health conditions are at higher risk for developing serious complications from influenza, including pneumonia, hospitalization, and mortality. Antiviral therapy is considered an important adjunct to vaccination in order to reduce the risk for severe illness from influenza among both adults and children, particularly those with underlying health conditions. Since the 2009 influenza A (H1N1) virus pandemic, both the Advisory Committee on Immunization Practices (ACIP), the Infectious Diseases Society of America, and the World Health Organization recommend early, empiric antiviral treatment for those with suspected or confirmed influenza who require hospitalization or have severe, progressive, or complicated illness, and for outpatients who are at higher risk for influenza complications based on age or underlying medical conditions [4–7]. Despite the burden of disease, there are limited data on how healthcare providers recognize influenza and adhere to treatment guidelines in clinical practice, particularly among high-risk populations. Additionally, to take advantage of these recommendations, high-risk persons with signs and symptoms of influenza must seek care promptly for assessment and possible antiviral treatment.

In this issue of The Journal of Infectious Diseases, Biggerstaff and colleagues report on the healthcare-seeking behaviors among persons with influenza-like illness (ILI) and the use of antiviral medications among adults, including those with high-risk conditions in outpatient settings during the 2010–2011 influenza season [8]. Data were analyzed from the Behavioral Risk Factor Surveillance System (BRFSS), a state-based, random-digit-dialed telephone survey, conducted in 31 states and DC from January to April 2011. Adults with underlying medical conditions were more likely to report ILI, but the majority did not seek care within 48 hours, and only adults with chronic obstructive pulmonary disease (48%) or heart disease (55%) were more likely to seek care within 2 days. Even among those who reported ILI, sought healthcare, and were diagnosed with influenza, only one-third (34%) reported receiving influenza antiviral medications according to ACIP recommendations, and those with underlying conditions were not more likely to receive antivirals. However, those patients who did seek care within 48 hours were more likely to report receiving antivirals than those who sought care later. Low use of antivirals among high-risk populations was similarly reported based on a BRFSS survey conducted during the 2009 pandemic [9].

Suboptimal adherence to treatment guidelines has been noted in other studies of high-risk patients, particularly in years since the 2009 H1N1 pandemic. Among populations with severe illness requiring hospitalization, use of antivirals among patients with laboratory-confirmed influenza, increased from prepandemic (51%–57%) to pandemic seasons (82%); however, fewer than half were treated within 48 hours, and by 2010–2011, the use of antivirals had decreased by 27% in children (to 56%) and by 6% in adults (to 77%) [10, 11]. Hernandez reported that, based on hospital discharge data, one-third of those hospitalized during the 2 pandemic waves did not receive antivirals; those that were tested were more likely to receive...
treatment [12]. Other studies have also shown that the use of antivirals among hospitalized patients has decreased since the pandemic and were underused among high-risk populations in emergency department and outpatient settings [13–16].

Lack of adherence to antiviral treatment guidelines likely involves clinical, economic, and social barriers. Challenges for providers include the accurate and timely diagnosis of influenza, lack of reliable rapid influenza diagnostic tests, and the late presentation of patients to clinical care [17, 18]. Antivirals are often not prescribed because of the uncertain diagnosis of influenza, as influenza commonly circulates with other viruses, making it difficult to clinically distinguish influenza from other acute respiratory infections [17, 18]. Older adults may have atypical presentations or present with decompensation of chronic medical conditions [17]. Availability of accurate and timely diagnostic tests is an important barrier. Data have shown that rapid influenza diagnostic tests have poor sensitivity compared to identifying influenza with reverse transcription polymerase chain reaction, with lower sensitivity among adults than children [19–21]. Biggerstaff and others have reported that those receiving antiviral treatment in the outpatient setting were more likely to have been tested and have positive rapid tests for influenza [8, 15]. False-negative results from rapid tests may lead to increased influenza morbidity due to lack of prompt initiation of antiviral treatment. Additionally, patients not tested are less likely to receive antivirals, suggesting that empiric treatment is limited [8].

Survey data among providers suggest concern about antiviral drug effectiveness and costs of treatment as possible additional barriers to the use of antivirals [22, 23]. Data on the efficacy of early treatment with antivirals (oral oseltamivir, inhaled zanamivir) come from randomized, placebo-controlled trials among healthy adults and children with uncomplicated illness, demonstrating that early treatment reduced fever and illness duration by approximately a day [7, 24–27]. Oseltamivir reduced antibiotic use among healthy adults in one systematic review [27], but not another [25], and reduced the risk of lower-respiratory-tract complications requiring antibiotic use in another review [28]. Additionally, zanamivir demonstrated a preventive effect on antibiotic usage in children.

Meta-analyses of observational studies suggest that antiviral treatment, primarily oral oseltamivir, reduced mortality in patients hospitalized with seasonal (odds ratio, 0.23; 95% confidence interval, .13–.43) [29] and 2009 H1N1 pandemic [30] influenza, and reduced hospitalization (odds ratio, 0.75; 95% confidence interval, .66–.89) and duration of illness, with greater clinical and virologic benefit associated with earlier initiation of treatment [29, 31–32]. However, even antivirals started after 48 hours of symptoms provided some benefit in severe infections [29, 31, 33–35].

Cost-effectiveness analyses among patients at increased risk of influenza complications generally find that antivirals are cost effective, although among some populations, effectiveness also depends on influenza prevalence and accuracy of diagnosis [27, 36–40]. However, several analyses report that any antiviral treatment is more cost effective than no treatment [38–40].

Future effectiveness data, particularly among high-risk populations, will likely be derived from high-quality observational studies or comparative effectiveness studies of new agents compared to standard of care, as placebo-controlled trials are no longer possible because of the perceived unethical nature of withholding antivirals from those at risk. Data on important patient clinical outcomes will be critical to assess effectiveness [41].

Provider concerns about the safety of antivirals and antiviral resistance may be other potential barriers. However, neuraminidase inhibitors have an excellent safety profile [4]. A recent review of systematic reviews reported that among healthy adults, nausea and vomiting were the most common adverse effects in oseltamivir randomized trials; in healthy adults and children, no significant adverse effects were noted in zanamivir treatment trials; and in children and at-risk individuals treated with oseltamivir or zanamivir, no serious adverse effects were found [24, 27]. Surveillance for adverse events related to antivirals during the 2009 pandemic was consistent with the known safety profile [42].

To date, oseltamivir resistance is low among circulating influenza viruses in the United States. Although resistance of influenza A (H1N1) viruses to oseltamivir has been documented, emergent resistance during treatment is uncommon, and global surveillance is ongoing [43].

Access to healthcare and other economic and social issues may be barriers for high-risk patients to seek healthcare when they have an ILI or an exacerbation of their underlying condition. In the Biggerstaff et al study, those without insurance, or who are unemployed or unable to work, were more likely to delay care or not seek care [8]. Lack of healthcare access may also impact receipt of antivirals. Similar findings were reported among outpatients seeking care during the 2009 pandemic [9]. Influenza hospitalizations have been associated with low census tract socioeconomic status [44, 45]. Further information is needed on the impact of healthcare access factors on healthcare-seeking behaviors and receipt of antiviral treatment.

Influenza will continue its annual onslaught of morbidity and mortality into the foreseeable future. Similarly, vaccination and antiviral treatment will remain the 2 best interventions at hand to mitigate the impact of these yearly epidemics. Although neither is a perfect solution, both have demonstrated effectiveness and both are underutilized. Improving the use of vaccines is a subject for another time. Here we ask what is needed to improve the suboptimal use of influenza antivirals among those at highest risk. Several elements of a solution suggest
themselves: more sensitive and specific (and inexpensive) point-of-care diagnostics, and more effectiveness studies of antivirals on meaningful clinical endpoints among high-risk patients (especially among those presenting for care beyond 48 hours after the onset of illness), as well as enhanced provider knowledge, attitude, and practice. In particular, we encourage empiric antiviral treatment of high-risk patients presenting with influenza-like illnesses during those times when influenza is known to be active in the community.

Notes

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References


