Comparing Clinical Characteristics Between Hospitalized Adults With Laboratory-Confirmed Influenza A and B Virus Infection

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We challenge the notion that influenza B is milder than influenza A by finding similar clinical characteristics between hospitalized adult influenza-cases. Among patients treated with oseltamivir, length of stay and mortality did not differ by type of virus infection.

**Keywords.** influenza A and B virus infection; antiviral treatment; hospitalization; adult.

Infection due to influenza B virus is often perceived to be milder than influenza A virus infection. However, studies have shown similar clinical features between patients infected with seasonal influenza A and B virus in outpatient settings [1, 2] and substantial influenza B infections among pediatric influenza-associated fatalities [3]. In addition, some studies have suggested that oseltamivir may be less effective at reducing fever in outpatients infected with influenza B virus compared with influenza A virus [4]; very few published studies have compared outcomes among hospitalized patients, especially among adults. We used 8 years of data from adults hospitalized with laboratory-confirmed influenza to compare clinical characteristics between those infected with influenza A and B viruses and to compare outcomes among patients treated with antiviral medications by virus type.

**METHODS**

We used data from 2005–2006 through 2012–2013 influenza seasons collected through the Influenza Hospitalization Surveillance Network (FluSurv-NET), a partnership between the Centers for Disease Control and Prevention (CDC) and state and local health departments, academic institutions, and their collaborators in multiple states. Prior to 1 September 2009, the following 10 states were included in surveillance: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. During 1 September 2009–30 April 2010, the following 5 additional states were included in surveillance: Iowa, Idaho, Michigan, Oklahoma, and South Dakota. After 1 October 2010, California, Colorado, Connecticut, Georgia, Idaho, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oklahoma, Rhode Island, Tennessee, and Utah were included in surveillance. FluSurv-NET conducts population-based surveillance for laboratory-confirmed influenza-associated hospitalizations during the influenza season (ie, 1 October to 30 April for regular influenza season; the 2008–2009 season, however, ended on 14 April to account for the emergence of the influenza A(H1N1)pdm09 virus in the spring of 2009; the 2009–2010 season encompassed 15 April 2009 through 30 April 2010). Patients were captured in the surveillance system if they resided in the project catchment area and were hospitalized in one of the surveillance hospitals with a positive influenza test result as determined by viral culture, immunofluorescence antibody staining, rapid antigen test, reverse transcription polymerase chain reaction, or documentation of a positive test result in a patient’s medical record. Demographic and clinical information were obtained from medical chart review. The analysis was limited to patients aged ≥18 years and excluded possible nosocomial infections.

In addition, we summarized influenza virus surveillance data from the World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System collaborating...
laboratories (CDC, unpublished data) for adults (aged ≥21 years) to describe type-specific distribution of influenza viruses circulating during each season included in this analysis.

We used t test and Wilcoxon rank-sum test to compare continuous variables (age and median length of stay) and \( \chi^2 \) tests and logistic regression to compare categorical variables (sex, presence of high-risk medical conditions, mechanical ventilation, intensive care unit [ICU] admission, bacterial coinfection, prolonged hospital stay [≥5 days], and death during hospitalization) by influenza type among younger adults (aged 18–64 years) and older adults (aged ≥65 years). We also compared mortality and length of hospitalization among patients who were treated with oseltamivir by virus type using unconditional logistic regression and Cox proportional hazards regression models; for this analysis we excluded the 2008–2009 season when there was widespread oseltamivir resistance among seasonal influenza A viruses [5]. Potential confounders such as ICU admission, presence of high-risk medical conditions, and age group were included to produce an adjusted hazard ratio. All statistical analyses were performed using SAS statistical software version 9.3 (Cary, North Carolina).

Collection of human subject data has been determined by the CDC to be routine public health surveillance and was not subject to institutional review board approval from human research protections.

RESULTS

We identified 23,186 (87%) influenza A and 3,579 (13%) influenza B virus–associated hospitalizations among adults from 2005–2006 through 2012–2013. Influenza A virus–associated hospitalizations predominated in every season with the highest proportion (99%) in the pandemic period and the lowest (66%) in the 2007–2008 season (Figure 1). The numbers of hospitalizations associated with both influenza A and B mirrored the prevalence of viruses in the community identified by the national influenza virologic surveillance each season. Despite the greater number of influenza A hospitalizations, there was no significant difference in the overall proportions of hospitalizations with an ICU admission by virus type for each season.

There were no significant differences between influenza A and B virus infections among hospitalized adults aged ≥65 years regarding presence of high-risk conditions, median length of hospitalization, admission to ICU, or death in the hospital. After adjusting for the presence of high-risk conditions, antiviral treatment, and seasonality, the adjusted odds ratio (aOR) for ICU admission was 1.05 (95% confidence interval [CI], .90–1.20), and for death was 0.89 (95% CI, .70–1.16). Adults aged 18–64 years hospitalized with influenza A virus infection were more often admitted to the ICU (OR, 1.36 [95% CI, 1.18–1.57]) than those with influenza B; however, the finding became null.
after adjusting for presence of high-risk conditions, antiviral treatment, and seasonality (aOR, 1.14 [95% CI, 0.98–1.33]). No significant difference in other parameters, including length of stay (P = .47) and death (aOR, 0.88 [95% CI, 0.75–1.08]) were detected in this age group.

Overall, 75% of all adults hospitalized with influenza received antiviral treatment. The use of antivirals increased from 54% pre-pandemic to 82% during and postpandemic. We identified 17,089 and 2200 adults infected with influenza A and influenza B viruses who received oseltamivir during the study period, respectively. Almost all (99%) patients were treated with oseltamivir, either alone or in combination with other influenza antiviral medications. The median length of hospital stay was 4 (interquartile range [IQR], 3–7) and 5 (IQR, 3–7) days among treated adults <65 and ≥65 years of age, respectively, and did not differ by type of influenza virus. Among oseltamivir-treated patients, we found no difference in the length of hospital stay by type of influenza virus infection (adjusted hazard ratio [aHR], 0.99 [95% CI, 0.98–1.07]). The results remained nonsignificant after stratification by age group (<65-year group: aHR, 0.98 [95% CI, 0.91–1.04]; and ≥65 age group: aHR, 1.01 [95% CI, 0.96–1.08]). Among treated patients, 508 (3%) with influenza A and 72 (3.3%) with influenza B died during hospitalization, and mortality was not associated with types of influenza virus infection (aOR, 0.91 [95% CI, 0.70–1.16]).

DISCUSSION

The number of hospitalizations associated with influenza A virus infections was greater than the number with influenza B virus infections, reflecting the greater prevalence of influenza A viruses circulating in the community during the seasons in the study period. Our results suggest that the clinical characteristics of hospitalized adults with influenza A and B virus infection, including length of stay, ICU admission, and death during hospitalization were comparable. Other studies have reported similar clinical characteristics between outpatients [2] and hospitalized children [1, 6, 7] with influenza A and B virus infections prior to the 2009 pandemic. However, some studies suggest that during seasons when A(H3N2) was the predominant subtype, outpatients with influenza A virus infection reportedly sought care earlier than patients with influenza B virus infection [2], and influenza-associated mortality estimates are reported to be the highest during A(H3N2)-predominant seasons [8]. We did not have subtype information available for most patients, limiting our ability to stratify the analysis by influenza A virus subtype. However, during most A(H3N2)-predominant seasons, we did not find a greater proportion of ICU admission among patients with influenza A compared with B virus infections. We only found a higher proportion of ICU admission among patients aged 18–64 years with influenza A virus infection during the 2010–2011 season, when A(H3N2) viruses predominated. However, there was co-circulation of A(H1N1)pdm09 virus, and patients infected with the A(H1N1)pdm09 virus strain were reported to have more severe outcomes than patients with A (H3N2) virus infection [9]. No increased severity in patients with influenza A was observed during the pandemic, which was likely due to the rare circulation of influenza B viruses during that period. Thus, our findings suggest that influenza B virus infections caused substantial morbidity among hospitalized adults and should not be regarded as a less severe infection than influenza A virus infection when considering treatment options.

Influenza B viruses have a higher baseline 50% inhibitory concentration (IC50) value for oseltamivir than influenza A viruses in vitro neuraminidase inhibition assays [10]. Some investigators have questioned whether this difference is associated with altered drug effectiveness. Also, observational studies have suggested that oseltamivir treatment may reduce fever more quickly with influenza A compared with influenza B virus infections [4]. Although we were not able to explore all clinical outcome differences, such as duration of fever or virus shedding, we found no differences in length of hospital stay and mortality that have been reported in observational studies of antiviral effectiveness among hospitalized patients [11, 12].

This study has limitations. The FluSurv-Net surveillance relies on clinicians ordering influenza testing. We do not know if testing practice has changed over time or whether physicians were more likely to test more severe hospitalized cases. Nonetheless, none of these limitations are likely to affect our results, as physicians cannot distinguish influenza type by signs and symptoms at presentation when ordering testing.

In conclusion, among hospitalized adults, influenza A and B infections resulted in similar morbidity and mortality. Antiviral treatment should be recommended for all hospitalized patients with suspected or confirmed influenza virus infection. Our results indicate that the type of influenza virus infection should not influence treatment decisions.

Notes

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