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Antiviral Research

Pre-and post-pandemic trends in antiviral use in hospitalized patients with laboratory-confirmed influenza: 2004/05–2013/14, Toronto, Canada

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ABSTRACT

Background: Data on factors associated with the use of antiviral medication to treat influenza in both children and adults are limited.
Objectives: To describe trends in antiviral use, analyze factors associated with antiviral treatment of hospitalized patients with influenza, and to compare use based on guidelines.
Study design: A retrospective observational cohort of hospitalized patients with laboratory confirmed influenza in southern Ontario hospitals for the 2004/05–2013/14 seasons.
Results: Of the 7967 patients, 18% of the 1779 children (<15 years) and 66% of the 6188 adults received antiviral therapy. The percentage treated increased from 29% pre-pandemic to 74% during the pandemic, decreased to 55% in 2011/12 and then increased to 65% in 2013/14. Factors significantly associated with antiviral prescription across all age groups during the non-pandemic seasons include influenza type, disease severity, interval between symptom onset and test sample submission, and clinician suspicion of influenza. Rate of treatment of patients meeting guideline criteria was low for children and moderate for adults.
Conclusions: Since the pandemic, there has been a sustained increase in the use of antiviral medication for all age groups of hospitalized patients with influenza, but much higher for adults than children. The odds of treatment are higher for patients with more severe disease as well as for those tested within 48 h of symptom onset, both of which are part of the guidelines for treatment with anti-influenza medications.

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1. Introduction

Illness caused by influenza viruses results in an estimated 3–5 million severe cases and 250,000–500,000 deaths annually (World Health Organization, 2014). Data from observational studies suggest that therapy with neuraminidase inhibitors improves outcomes for patients with laboratory confirmed influenza (Muthuri

et al., 2014). In Canada, guidelines for the use of antiviral therapy were first introduced in 2006. They recommended treatment for people one year of age and older who were severely ill with influenza but reserved treatment initiated more than 48 h after symptom onset for immunocompromised patients with progressive respiratory illness (Allen et al., 2006). In 2012, the recommendation for therapy was broadened to include people whose illness was severe enough to require hospital admission and for all people at high risk of complications from influenza (Aoki et al., 2012). Despite these recommendations, and similar recommendations in the USA (Harper et al., 2009), studies have described a significant decline in the use of antiviral medication for treating influenza following the 2009 pandemic (Garg et al., 2012; Taylor et al., 2014).

We undertook this study to describe the use of antiviral medication in hospitalized patients with laboratory-confirmed influenza between 2004/05 and 2013/14 in Toronto, Canada, and to assess factors associated with antiviral therapy.

2. Materials and methods

2.1. Study design

During the 2004/05–2013/14 influenza seasons, all hospitals providing service to residents of metropolitan Toronto and Peel region (i.e. members of the Toronto Invasive Bacterial Diseases Network; N = 21 hospital corporations) participated in surveillance for laboratory-confirmed influenza illness requiring hospitalization (McGeer et al., 2007). Eligible patients were those with influenza identified in a respiratory specimen who required admission for or who were hospitalized at the time of the positive test result. Study staff screened laboratory results [culture, direct fluorescent antigen (DFA) detection, enzyme immunoassay (EIA), or polymerase chain reaction (PCR)] to identify eligible cases, approached patients or their substitute decision makers for consent, and collected demographic and medical data by patient and physician interview and chart review. This study was approved by the ethics review boards of all participating hospitals. Neither laboratory protocols nor physician prescribing practice were altered for the study.

2.2. Clinical data and definitions

The primary outcome was the prescription of any antiviral drug active against influenza for the episode of infection (prior to or during hospital stay). Influenza seasons were defined as from September 1st to August 31st each year except during the 2009 pandemic which was defined as starting May 19, 2009 (World Health Organization, 2009). It was decided *a priori* to stratify into three periods: pre-pandemic (2004/05–2008/09), pandemic (2009/10), and post-pandemic (2010/11–2013/14) and three age groups: children (<15 years), younger adults (15–64 years), and older adults (65 years and older). Original text entries of admitting diagnoses were categorized as influenza suspected at admission if the words influenza, flu, or H1N1 was included. Charlson, APACHE II, and Glasgow coma scores were based on data available within 24 h of testing for nosocomial cases and 24 h of admission for community-associated cases. Influenza-like illness (ILI) was defined as ≥1 of fever, myalgia, or arthralgia and ≥1 of cough, runny nose, or sore throat or an admitting diagnosis containing the words influenza, flu, or H1N1. Progressive or severe influenza disease was defined as per the 2010 Canadian treatment guidelines (Aoki et al., 2010). We assessed the extent to which prescribers followed Canadian Association of Medical Microbiology and Infectious Disease (AMMI) guidelines published in 2006 (Allen et al., 2006) and 2010 (Aoki et al., 2010) and the Infectious Diseases Society of America

(IDSA) guidelines published in 2009 (Harper et al., 2009).

2.3. Statistical analysis

Multivariable logistic regression analyses stratified by each of the three periods and three age groups assessed factors (see Table 1) associated with antiviral treatment (any versus none). Models were built using a purposeful selection procedure (Hosmer and Lemeshow, 2000) that included variables with a *p*-value of <0.10 and potential confounders changing the parameter estimates by >15%. Because of the multiplicity of underlying chronic medical conditions, the primary multivariable analysis used the Charlson comorbidity index as the measure of underlying illness. A sensitivity analysis using the major chronic underlying illnesses listed in Table 1 was conducted. Hospital site was included as a potential confounder in all models. Collinearity was assessed with the more clinically plausible variable maintained, when necessary. Models were assessed for outliers, effect moderation, and goodness of fit using Stata SE v11.2 (StataCorp, 2009).

3. Results

During the 10 influenza seasons (2004/05–2013/14), 7967 of 8462 (94%) eligible cases consented to the study; 5925 (74%) with influenza A and 2042 (25%) with influenza B (Table 1). Overall, influenza was diagnosed in 6164 by PCR, 1429 by culture, 329 by EIA, and 45 by DFA. There was a shift to PCR testing over the study period, with 20% of tests being done by PCR in the pre-pandemic period compared with 88% during the pandemic and 95% post-pandemic (p < 0.001). Influenza B accounted for 30% of cases (N = 2041) in the pre- and post-pandemic periods, and 1 case (0.1%) during the pandemic season.

The study included 1779 children (<15 years), 2424 younger adults (15–64 years), and 3764 seniors (≥65 years). The median age of patients was 62 years (range 1 week–105 years) and 50% were female. During the pandemic, infected children were significantly older (median 4.1 vs 2.0 years; p < 0.001) while infected adults were significantly younger (47 vs 75 years; p < 0.001) than in other seasons.

The most common underlying medical condition was underlying pulmonary disease/asthma (2627 or 33%), followed by diabetes (21.7%) and neurological/neuromuscular conditions (18.2%) (Table 1). Of the 7494 patients with community-associated disease, only 1031 (13.8%) had an admission diagnosis of suspected influenza; however an additional 60% (4508) had an admission diagnosis including a respiratory diagnosis (e.g. pneumonia, COPD exacerbation) or symptom (e.g. shortness of breath). In total, 40.8% of patients were tested for influenza within 48 h of symptom onset including 99.4% of nosocomial cases and 80.1% of the 3430 patients admitted within 48 h of symptom onset.

3.1. Temporal trends in antiviral use

All 324 children who received antivirals were prescribed oseltamivir as were 4059 (98.7%) adults. Other adults received zanamivir (n = 8), amantadine (n = 4), or some combination of the three drugs. None of the 42 multi-antiviral treatment regimens occurred prior to the 2007/08 season.

As shown in Fig. 1, the percentage of patients who received antivirals did not vary significantly in the pre-pandemic seasons (29.0%; p = 0.20), increased dramatically during the pandemic to 73.6% (p < 0.001), declined sharply over the subsequent two seasons to 54.7% (p < 0.001), then increased again to 65.4% (p < 0.001) in 2012/13–2013/14. The pattern was similar across all age groups with 1.4% (95% CI 0.4,2.4) of children treated prior to the pandemic,