FACTORS ASSOCIATED WITH MORTALITY IN SEVERE DISEASE DUE TO INFLUENZA IN ADULTS IN TORONTO, CANADA 2005-2008

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Abstract (revised)

Background: Few data describe the outcomes of severe influenza (S-FLU). In previous surveillance, predictors of S-FLU mortality were the Charlson index, admission to ICU, nursing homes residence, short duration of illness prior to admission, and the absence of antiviral therapy (Rx). However, our sample size in the previous study was small and associations might have occurred by chance. We report the results of on-going surveillance to assess risk factors for S-FLU mortality.

Methods: Since 1/1/2005, TIBDN has performed population-based surveillance for laboratory-confirmed influenza requiring hospitalization in Toronto/Peel (pop 4.5M). Patients hospitalized for illness associated with a positive influenza antigen test, culture or PCR were enrolled.

Results: From 1/2005 to 5/2008, 1134 adult patients with S-FLU were enrolled (807 with influenza A and 326 with influenza B). Median age was 77.6 years (range 15-101y). 555 (49%) were male. The median Charlson index was 1 (range 1-12). 597/947 (63%) had received the influenza vaccine. 165 (15%) were nursing home residents. 52 patients (4.6%) had a concurrent bacterial infection (28 *S. aureus*, 15 *S. pneumoniae*, 3 *E. coli*, *2 H. influenzae*, 2 *M. catarrhalis*, 1 Group A *Streptococcus*). 208 (18%) required ICU admission. Median LOS was 7 days (range 1-103d). 649 (82%) pts received antibiotics, while 429 (38.7%) received antivirals (3 amantadine, 426 oseltamivir). 292/380 (76%) who were treated with oseltamivir received their 1st dose >48h after symptom onset. 15d mortality was 8.7% (96/1099). In the multivariate analysis, ICU admission (OR 7.95, 95% CI 4.62,13.68, P<.0001), nursing home residence (OR 3.21, 95% CI 1.76,5.83, P<.0001), and failure to treat with antivirals (OR 2.13 95% CI 1.19, 4.5, P=.01) were associated with death.
Conclusions: Seasonal influenza is a significant cause of serious illness. Oseltamivir treatment significantly reduces mortality in severely ill patients even when therapy is started >48 hours after the onset of symptoms.

Introduction

Annual influenza outbreaks have long been acknowledged as an important cause of high morbidity and mortality, especially among the extreme ages, people with chronic underlying illnesess, and the immunocompromised. While infants are vulnerable to influenza because of the immaturity of their immune systems and lack of previous exposure, older adults (>65 yrs old) suffer more consequences of influenza such as pneumonia, secondary bacterial infections, exacerbation of asthma and COPD, and cardiac complications) because of their aging immune response and chronic medical conditions. Residents of long term care facilities are at increased risk because of their older age, high incidence of underlying chronic illness, poor response to vaccination, and the ease of influenza transimssion in the residence. Since more than 90% of influenza-associated deaths occur in subjects over 65 years of age, the diagnosis and early treatment of influenza have the potential to play a significant role in health outcomes in this age group. The purpose of this study was to identify risk factors associated with mortality in adult influenza cases requiring hospital admission.

Figure 1:
TIBDN population area

Methods

A population-based surveillance study of laboratory-confirmed influenza requiring hospitalization in Metropolitan Toronto and Peel Region, Ontario, Canada, conducted by the Toronto Invasive Bacterial Diseases Network (TIBDN), began on January 1 2005. TIBDN is a network comprising all hospitals and microbiology laboratories serving the population of Metropolitan Toronto and Peel region (pop. 4.5 million in 2006).

All influenza cases were reported to the TIBDN study office where a study number was assigned and initial clinical and microbiology information was collected. All hospitalized cases were forwarded to study nurses to obtain consent, to collect clinical and laboratory data from patient charts and family doctors, and to conduct a short interview with patients. Nasopharyngeal swabs were taken in ER, ICU and medical departments and were processed in site microbiology labs using rapid tests (EIA, DFA) or culturing. Most of the samples were sent to Ontario Public Health Laboratory for further RT-PCR testing, culture and subtyping. During the 2006-2007 flu season we did active surveillance in the ICU departments of 6 TIBDN hospitals, and during the 2007-2008 flu season we added to this surveillance all medical admissions at 4 of these hospitals. At the end of the flu season an audit was conducted to better capture all influenza cases. We have used Charlson Index as a prognostic indicator for clinical outcomes of adult patients with comorbid conditions since it correlates significantly with mortality, disability, readmission and length of hospital stay. We have looked as well at bacterial co-infections, rate of flu vaccination, use of antibiotics and time of initiation of antivirals.

All data were entered, processed and analyzed using SAS version 9.1 and odds ratios were calculated with 95% confidence intervals. Prior research ethics board approval for the study was obtained from all participating hospitals.

Results (updated)

From 1/2005 to 5/2008, 1134 adult patients with S-FLU have been enrolled (we have complete data on 1092 of them). Comparing data between patients who died and patients who survived resulted in the following conclusions: there were no differences in gender between the two groups (49 % of survivors were males, and 50 % of those who died); grouping patients by age showed that patients over 65 years old comprised 84.4 % of deaths compared to 5.2 % of deaths for the age group 15-44 yrs old. Median Charlson index was 1 (range 1-8) and the higher the Charlson score the higher the fatal outcome; 34.4 % of patients who died were residents of nursing homes compared to 13% of the survivors. 52 patients out of 1134 (4.59%) had an identified bacterial co-infection (28 *S. aureus*, 15 *S. pneumoniae*, 2 *H. influenzae*, 1 group A streptococcus, 3 *E. coli*, 1 *M. catarrhalis*). 49(52%) of 96 patients who died required ICU admission compared to 154 (15.4%) of patients who survived. Median LOS was 7d (range 1-103d). 91% of patients who died received antibacterial Rx, compared with 81% in survivors. 395 (39.6%) of survivors received antiviral Rx compared to only 26 (27.1%) in the group of patients who died; 76% of oseltamivir-treated patients received their 1st dose >48h after symptom onset. 15d mortality was 8.7% . In multivariable analysis, ICU admission (OR 7.95, 95% CI 4.62,13.68, P<.0001), nursing home residence (OR 3.21, 95% CI 1.76, 5.83, P<.001), and failure to treat with antivirals (OR 2.13 95% CI 1.19, 4.5, P=.01) were associated with death.

Results (con't)

Table 1:Total number of cases: 1131 adults (>15 yrs of age) over 4 seasons

Characteristic	Survived N=1002	Died N=96	P value
Sex (% male)	491 (49%)	50 (52%)	.59
Age group 15-44 years 45-64 years 64-74 years 75-84 years >=85 years	 126 (12.5%) 151 (15.1%) 165 (16.5%) 326 (32.5%) 234 (23.4%)	 5 (5.2%) 10 (10.4%) 17 (17.7%) 36 (24.5%) 28 (29.2%)	.01
Charlson score 0 1 2 3 >=4	 212 (21.2%) 301 (31.0%) 225 (22.5%) 168 (16.8%) 86 (8.6%)	 11 (11.6%) 22 (23.2%) 18 (19.0%) 21 (22.1%) 23 (24.1%)	<.0001
Source of influenza Community Nursing Home Hospital	 130 (13.0%) 145 (14.5%)	 33 (34.4%) 13 (13.5%)	<.0001
Received influenza vaccine this season*	542 (62.2%)	50 (72.5%)	.09
Required ICU admission	154 (15.4%)	49 (52%)	<.0001
Smoker	112 (11.1%)	15 (15.6%)	0.4
Influenza type (% A)	713 (71.1%)	69 (71.9%)	.87
Season 2004/5 2005/6 2006/7 2007/8	 285 (28.0%) 99 (10.0%) 161 (16.1%) 457 (45.65%)	 28 (29%) 6 (6.3%) 19 (19.8%) 43 (44.8%)	0.55
Treated with antibiotics**	581 (81%)	62 (91%)	.05
Treated with antiviral	395 (39.6%)	26 (27.1%)	0.2
Laboratory confirmed bacterial co-infection	39 (3.81%)	11 (11.5%)	.003

Complete data available for 1092
129/1098 died during hospitalization (11.7%); 96 (8.7%) died within 15 days of symptom onset
*Data on Influenza vaccine available for 941 patients
** Data on antibiotic therapy were not collected in the first year of the study

Table 3: Distribution of pathogens in the 52 (4.6%) laboratory confirmed bacterial infections complicating severe pneumonia

Pathogen	Number of infections	Percent
Staphylococcus aureus	28	54%
Streptococcus pneumoniae	15	29%
Escherichia coli	3	6%
Haemophilus influenzae	2	4%
Serratia marcescens	2	4%
Streptococcus pyogenes	1	2%
Moraxella catarrhalis	1	2%

Results (con't)

Table 2

	Survived	Died	P value
Age (median, range)	77.6 (15-100)	80.8 (17, 100)	.005
Charlson co-morbidity score (median, range)	1 (0.12)	2 (0,8)	<.0001
Apache score (median, range)	14 (0.37)	20 (8,42)	<.0001
Hours from onset of symptoms to emergency department registration (median, interquartile range)	39 (14, 73)	22 (6.3,39)	.002

Table 3: Results of multivariable analysis of predictors of 15 day mortality in patients requiring hospitalization influenza

Characteristics	Odds Ratio (955 CL)	P value
Age (odds ratio per decade)	1.3 (.11, 1.5)	.04
Required ICU admission	8.0 (4.6, 13.7)	<.0001
Resident of nursing home	3.2 (1.8, 5.8)	.0001
Charlson co-morbidity score (per point)	1.2 (1.0, 1.4)	.01
Not treated with antiviral	2.1 (1.2, 4.5)	.01
Timre from symptoms onset to ED registration (pre 24h)	0.85 (0.73, 0.98)	.03

In subset analyses, there was no difference in the estimated odds ratio for survival compared to no therapy antiviral therapy for patients who received their first dose of oseltamivir ≤48 hours after the onset of symptoms or for those who received their first dose>48 hours after symptom onset.

Conclusions:

Seasonal influenza is a significant cause of serious illness. Oseltamivir treatment significantly reduces mortality in severely ill patients even when therapy is started >48 hours after the onset of symptoms.

Acknowledgments:

The success of this surveillance is due to the contributions of many staff of TIBDN hospitals, public health units, and microbiology laboratories, as well as the patients, their families and attending and family physicians. We thank all of them. We are also grateful for the tireless work, careful thought and enthusiasm of the core TIBDN staff.