Epidemiology and clinical features of severe influenza in adults: 7 years of surveillance in Toronto, Canada

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Introduction and Purpose

The epidemiology of influenza illness requiring ICU admission in adults has not been well studied. Here we describe the results of surveillance for influenza in adult patients requiring intensive care in Toronto, Canada over 7 Influenza seasons by the Toronto Invasive Bacterial Disease Network (TIBDN). TIBDN is a network of hospitals and microbiology laboratories that conduct population-based surveillance for infectious diseases in metropolitan Toronto and Peel region (pop. 4 million). Since December 2004, TIBDN has conducted active surveillance for patients with laboratory confirmed influenza (LCI) who require hospital admission (ICU and non-ICU). Each year influenza causes significant morbidity and mortality, particularly among patients at the extremes of age, and those with chronic underlying medical and immunocompromising conditions. The objectives of this analysis were to determine the incidence of influenza requiring ICU admission in our population, to describe the clinical features of infection and to identify risk factors for fatal outcomes.

Methods

Population-based surveillance for laboratory confirmed influenza in adults (> 15 yrs) requiring ICU admission (LCI-ICU) in Toronto/Peel (pop 4M) was performed from December 2004 to May 2011 (7 influenza seasons). Consenting patients with a positive direct test (antigen or PCR) or culture for influenza were enrolled. From the 2006/7 season to the 2010/11 season, active surveillance for influenza was conducted in 7 of 23 ICUs in the surveillance area.

Nasopharyngeal swabs, and some sputum and BAL samples were processed in licensed microbiology labs using EIA , PCR and/or culture. EIA testing was confirmed by culture or PCR whenever possible. From 2007/8 on, all samples were sent to Ontario Public Health Laboratory for viral typing. Annual audits were conducted to ensure completeness of reporting.

Clinical data, including APACHE II score at ICU admission and Charlson co-morbidity score were collected from all patients. Bacterial co-infections were defined as occurring when a pathogenic bacteria was isolated from blood or a respiratory specimen at the time of presentation. Effective antivirals were defined as antivirals to which the influenza subtype was likely to be susceptible during that season (e.g. amantadine was effective against sH1N1 before 2006).

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

Results

From December 2004 to May 2011, 576 adults (≥15 yrs) requiring ICU admission for community-acquired influenza were identified: 163 due to 2009 pH1N1 and 413 due to seasonal influenza (157 Influenza A/H3N2, 133 Influenza A (not subtyped), 11 Influenza A/sH1N1, 35 A/pH1N1 during the 2010/11 season, and 77 Influenza B).

The median annual incidence of influenza infection requiring ICU admission was 2.2/100,000 (range 0.38-4.3).

Table 1 : Characteristics of 576 adult influenza cases requiring ICU admission, 2004 to 2011.

Characteristics	N=576
Male gender	297 (51%)
Median age (range)	65 yrs (17-101)
Long term care resident	57 (10%)
Underlying health condition creating risk for influenza complications	472 (82%)
Chronic cardiac illness	222 (47%)
Coronary artery disease	114 (25%)
Congestive heart failure	79 (17%)
Arrythmia	60 (14%)
Chronic pulmonary illness	240 (51%)
COPD	121 (28%)
Asthma	97 (22%)
Diabetes mellitus	186 (40%)
Chronic renal failure	41 (9%)
Malignancy (any)	77 (16%)
Smoker	116 (20%)
Morbid obesity	24 (5%)
Median Charlson comorbidty score (range)	4 (0-13)
Received influenza vaccine >2 weeks prior to illness onset	153 (27%)
Diagnosis on admission to ICU:	
Influenza	42 (7%)
Pneumonia	189 (33%)
Other respiratory	134 (23%)
Cardiac	96 (17%)
Other	115 (20%)
Median APACHE II score at admission to ICU (range)	15 (2-42)
Influenza A	499 (87%)
Pandemic H1N1	163 (28%)
Treated with effective antiviral	380 (66%)
Effective antiviral received ≤ 48 hrs after symptom onset	61 (11%)
Bacterial co-infection	79 (14%)
Concomitant bacteremia	32 (6%)
Treated with antibiotics	522 (91%)
Median length of ICU stay (range)	6 days (1–134)
Mechanically ventilated	317 (55%)
Median length of mechanical ventilation (range)	8 days(1-88)
15 day mortality	107 (19%)
In hospital mortality	156 (27%)

Table 2: Bacterial pathogens identified in patients with laboratory-confirmed concomitant bacterial infections at admission

Pathogen	All infections	Bacteremia
Staphylococcus aureus	32 (5 MRSA)	15 (3 MRSA)
Streptococcus pneumoniae	32	15
Streptococcus pyogenes	6	1
Haemophilus influenzae	6	3
Pseudomonas aeruginosa	5	0
Escherichia coli	3	3
Klebsiella pneumoniae	2	1
Moraxella catarrhalis	1	0

Acknowledgements

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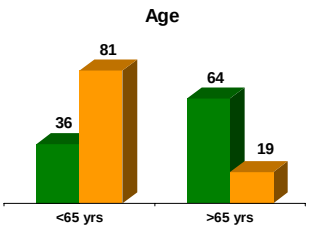
Results (Cont'd.)

Table 3 : Comparison of different characteristics among pandemic and seasonal influenza cases.

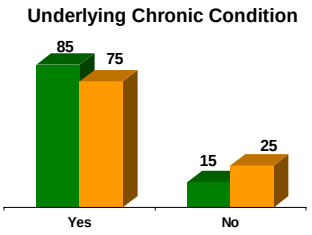
Characteristics	Pandemic (N=163) n/ (%)	Seasonal (N=413) n/N (%)	*p value*
Male gender	80 (49%)	217 (52%)	0.45
Age <65 yrs	132 (81%)	149 (36%)	<0.001
Resident of long term care facility	8 (5%)	49 (12%)	<0.01
Any underlying health condition	122 (75%)	350 (85%)	<0.007
Charlson comorbidity score ≥ median of 4	49 (30%)	249 (60%)	<0.0001
Vaccinated against influenza	1 (0.6%)	152 (37%)	<0.0001
APACHE II Score at ICU admission > median	76 (47%)	226 (55%)	0.09
Bacterial co-infection	19 (12%)	60 (15%)	0.42
Bacteremia	6 (4%)	26 (6%)	0.31
Treated with antibiotics	154 (94%)	368 (89%)	0.05
Treated with effective antiviral drug	143 (88%)	237 (57%)	<0.0001
Required mechanically ventilation	98 (60%)	219 (53%)	0.12
Died within 15 days of admission	29 (18%)	78 (19%)	0.76

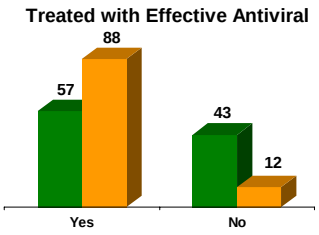
Fig. 1: Significant differences between seasonal influenza (green) and pandemic influenza (orange)



Patients with pandemic influenza were significantly younger than those with seasonal influenza, less likely to be residents in long term care facilities, and less likely to have a chronic underlying illness predisposing them to complications of influenza. They also had lower Charlson co-morbidity scores.

Patients with pandemic influenza were more likely to be treated with antibiotics and antivirals at admission. In unadjusted analysis, there was no difference in the proportion requiring mechanical ventilation or the case fatality rate in patients with pandemic and seasonal influenza.





In univariate analysis, older patients, nursing home residents and patients with higher Charlson co-morbidity scores, higher Apache II scores at admission, and bacterial co-infection were significantly more likely to die.

In multivariable analysis (see Table 4), older age, residence in long term care, pandemic influenza infection, higher Apache II score at admission and requirement for mechanical ventilation were associated with death.

Although only 16% of patients who received antivirals were treated within 48 hours of symptom onset, treatment with antivirals was associated with improved survival. We were unable to detect a difference in survival between those who received antivirals early and those who received them later, but our analysis is not adequately powered to rule out such an effect. Similarly, although we were unable to detect an effect of bacterial co-infection on mortality, the point estimate for the odds ratio for mortality was 1.6 (95% CI 0.84-2.9); our analysis may simply be underpowered to detect this effect.

Table 4: Characteristics of influenza cases and their association with 15 day mortality

Characteristic	15 day mortality Present n/N(%)	15 day mortality Absent n/N(%)	Odds Ratio for Mortality (95% CI) Univariable	Odds Ratio for Mortality (95% CI) Multivariable
Male gender	55 /297 (18%)	52/279 (19%)	1.0 (0.6-1.5)	
Age >65 yrs	72/295 (24%)	35/281 (12%)	2.3 (1.5-3.5)*	2.1 (1.2-3.5)
Long term care resident	19/57 (33%)	18/519 (17%)	2.4 (1.3-4.4)*	2.1 (1.0-4.2)
Underlying health condition	92/472 (19%)	15/104 (14%)	1.4 (0.8-2.6)	
Charlson comorbidity score > median	72/298 (24%)	35/278 (13%)	2.2 (1.4-3.4)*	
Vaccinated against influenza	32/153 (21%)	75/423 (18%)	1.2 (0.8-1.9)	
APACHE II Score > median	84/302 (28%)	23/274 (8%)	4.2 (2.6-6.9)*	3.6 (2.2-6.0)
Influenza Type A	90/499 (18%)	17/77 (22%)	1.3 (0.7-2.3)	
pandemic H1N1	29/163 (18%)	78/413 (19%)	1.1 (0.7-1.7)	1.9 (1.1-3.5)
Treated with effective antiviral	57/380 (15%)	50/196 (25%)	0.5 (0.3-0.8)*	0.41 (0.24-0.68)
Bacterial co-infection	23/79 (29%)	84/497 (17%)	2.0 (1.2-3.5) *	
Bacteremia	9/32 (28%)	98/544 (18%)	1.8 (0.8-4.0)	
Treated with antibiotics	101/522 (19%)	6/54 (11%)	1.9(0.8-4.6)	
Required mechanical ventilation	80/317 (25%)	27/259 (10%)	2.9 (1.8-4.6)*	2.7 (1.6-4.6)

Conclusion

Influenza is an important cause of respiratory illness requiring ICU admission during the winter season in Ontario. Approximately one sixth of influenza cases requiring ICU admission had laboratory confirmed bacterial co-infection, most commonly due to *S. aureus* or *S. pneumoniae.* Age, severity of illness at admission to ICU, residence in long term care and infection with pH1N1 during the pandemic were associated with increased 15 day mortality. Treatment with an effective antiviral was associated with a significant reduction in mortality.