

Influenza A or B virus infection 2012-2013: incidence, characteristics and outcome in critically ill patients in two Dutch intensive care units

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Keywords – critically ill adults, > 65 years, influenza A or B virus infection, COPD, bacterial super infection

ABSTRACT

Introduction: The flu epidemic of 2012-2013 was by far the longest in the past 20 years. In the whole country, beds in intensive care units (ICUs) were occupied by patients with flu symptoms. **Objective:** The aim of this study was to describe the incidence of influenza-related ICU admission, demographic characteristics, clinical features and outcome of confirmed influenza A/B infection in critically ill patients admitted to our ICUs during the winter of 2012-2013. **Methods:** A retrospective, observational multicentre cohort study was conducted in two Dutch ICUs. A polymerase chain reaction (PCR) analysis was only done in patients with flu symptoms. All critically ill adults with confirmed influenza A or B virus infection admitted between December 2012 and April 2013 were studied. **Results:** During the study period 1314 patients were admitted to the ICU. A total of 111 PCR analyses were performed; 19 were positive for influenza A and 16 for influenza B. The majority of the patients were over the age of 65 and had COPD and/or a bacterial super infection. Mean ICU mortality was 28.6% as predicted by SAPS II, APACHE II and PSI score. No statistically significant differences between survivors and non-survivors were found with respect to disease severity, positive vaccination status, comorbidities and duration of ventilation. Three months after the study all remaining patients were still alive. **Conclusion:** During the long flu epidemic in the winter of 2012-2013 especially older patients who had COPD and/or a bacterial super infection were most affected. Mortality was not associated with positive vaccination status.

Introduction

With 18 weeks (17 December 2012 – 21 April 2013), the flu season of 2012-2013 was by far the longest in the past 20 years.¹ Its peak incidence was 160 new influenza-like diseases per 100,000 inhabitants weekly.¹ Nevertheless, the National Institute of Public Health and Environment spoke of a relatively

mild influenza epidemic.² In 2009, the swine flu influenza A (H1N1) caused a global commotion, because the new influenza virus seemed to be much more dangerous than regular flu viruses. However, in the Netherlands very few people with flu symptoms and a positive polymerase chain reaction (PCR) for H1N1 were admitted to the ICU. In the 2012-2013 season, there were still some cases of flu caused by this type, but the majority of cases were caused by other variants such as the influenza A (H3N2) and influenza B virus. In the whole country, beds in intensive care units (ICUs) were occupied by patients with flu symptoms and confirmed influenza A or B virus infection. The aim of this study was to describe the incidence of influenza-related ICU admission, demographic characteristics, clinical features and outcome of laboratory-confirmed influenza A or B infection in critically ill patients admitted to our ICUs during the winter of 2012-2013.

Materials and methods

A retrospective, observational multicentre cohort study was conducted in two Dutch ICUs: a 30-bed mixed medical/(neuro) surgical ICU of St. Elisabeth Hospital and a 12-bed mixed medical/surgical ICU of Tweesteden Hospital. A PCR analysis was only done in patients with flu symptoms (such as fever, cough and/or dyspnoea). We studied all critically ill patients above the age of 16 years with confirmed influenza A or B virus infection who were admitted between December 2012 and April 2013. Influenza A and B were confirmed by means of a PCR assay. PCR assays were conducted at the laboratory of St. Elisabeth Hospital. Data of demographics (gender, age, body mass index, economic status, vaccination status, comorbidity, reason of admission and use of antibiotics at admission) and clinical symptoms and findings were recorded. Laboratory assessment included leukocytes, and C-reactive protein (CRP). We collected respiratory and blood cultures from each patient. Type and duration of mechanical ventilation,

PaO₂/FiO₂ at admission and also the use of vasopressors were recorded. Severity of illness was established using the Acute Physiology and Chronic Health Evaluation II and IV (APACHE II and APACHE IV) scores, APACHE IV mortality rate and by using the Simplified Acute Physiology score II (SAPS II). The Pneumonia Severity Index (PSI) and CURB-65 score assessed pneumonia severity. At the end of the study we determined mortality (ICU and hospital) and length of stay in the ICU and hospital. We also recorded discharge destination. During follow-up, we noted the rate of re-admission and 3-month mortality. We notified the local medical ethics committee about this study. Patient identification remained anonymous and informed consent was waived at all sites due to the retrospective and observational nature of the study.

Data management

We collected data by means of electronic and paper case report forms. Patients transferred between ICUs were counted as a single ICU admission. We made no assumptions regarding missing data: all proportions were calculated as percentage of the patients with available data.

Statistical analysis

Descriptive data were presented as frequencies (percentages). Median with interquartile range (IQR) was used for continuous variables that were not normally distributed. The non-parametric Mann-Whitney U test was performed to compare the characteristics between survivors and non-survivors in both ICUs. A two-sided P-value of < 0.05 was considered to be statistically significant. The statistical analyses were conducted using GraphPad PRISM 5.0 for Mac/Windows (Graphpad Software Inc. San Diego, CA, USA) and SPSS 18.0 (IBM Corporation, Inc. SPSS, Chicago, USA).

Results

Demographics

Between December 2012 and April 2013, 1314 patients were admitted to the ICU. A total of 111 PCR analyses for influenza A and B were performed, 19 (21%) of which were positive for influenza A and 16 (18%) for influenza B. Demographic characteristics are presented in *table 1*. The median age was over 65 years; slightly more than half of the patients were male. About one-third of the patients were vaccinated. Chronic obstructive pulmonary disease (COPD) was present in more than half of the cases, with an exacerbation of COPD and pneumonia as main reasons of ICU admission. Less than 10% of the patients were using antibiotics at the time of admission.

Clinical characteristics

Clinical characteristics are shown in *table 2*. Dyspnoea was seen in almost all patients and cough and fever in more than half of the patients. Leukocyte count and CRP were moderately

Table 1. Demographics

	All (n = 35)
Gender, (male/female)	20/15
Age (median [IQR])	68 [59-79]
Body mass index (kg/m ²) (median [IQR])	24.68 [22.94-26.04]
SES '10* (median [IQR])	-0.3221 [-1.086 – 0.504]
Positive vaccination status (%)	77.1
Comorbidity (n = [%])	
Diabetes	3 [8.6]
COPD	20 [57.1]
Heart failure	0 [0.0]
Chronic renal insufficiency	3 [8.6]
Immunosuppression	5 [14.3]
Cancer	7 [20.0]
Reason of admission to ICU (n = [%])	
Pneumonia (viral/bacterial)	11 [31.4]
Emphysema/bronchitis	11 [31.4]
Sepsis/shock	7 [20.0]
Congestive heart failure	3 [8.6]
Others	3 [8.6]
Disease severity (median [IQR])	
SAPS II score	43 [36-47.5]
Apache II score	20 [16-24]
Apache IV score	63 [50.5-77.5]
Apache IV mortality rate	0.215 [0.120-0.303]
PSI score	127.5 [104.25-150.25]
CURB-65 score	2.0 [1.0-2.50]
Use of antibiotic at admission (n = [%])	3 [8.6]

* SES '10 = Social economic status: a higher score corresponds to a higher socioeconomic status
Data are presented as median ± interquartile range (IQR) or as frequencies (percentages)

elevated. Clinical evidence of secondary bacterial infection was found in one-third of the cases, with *Staphylococcus aureus* and *Streptococcus pyogenes*, respectively, as the most common pathogens. All patients, except one, received mechanical ventilation; 13 patients who received non-invasive ventilation ultimately required invasive ventilation. The median ratio of PaO₂ to FiO₂ at admission was in the range of acute lung injury (ALI) and nearby the range of diagnosing acute respiratory distress syndrome (ARDS).

Outcome and follow-up

Data of outcome are presented in *table 3*. Vasopressors (norepinephrine) were administered in more than half of the patients with a median dose of 3.61 mg/day [IQR: 2.05-6.36] during ICU admission. Patients affected with the influenza A or B viruses were admitted to the ICU for 4.18 days with a median length of stay in hospital of 12.57 days. Among 35 critically ill patients with PCR-positive influenza A or B virus infection, about 28% of the patients died in the ICU; more than half of these patients were male. This corresponds to the SAPS II of 43, APACHE II score of 20 and the PSI score in pneumonia

Table 2. Clinical characteristics

	All (n = 35)
Clinical symptoms (n = [%])	
Cough	19 [54.3]
Dyspnoea	34 [97.1]
Fever	19 [54.3]
Nausea/vomiting	1 [2.9]
Diarrhoea	2 [5.7]
Altered mental status	6 [17.1]
Clinical findings (n = [%])	
Fever*	5 [14.3]
Respiratory rate ≥ 20 /min	24 [68.6]
Hypotension/hypertension [#]	11 [31.4]
Heart rate (< 60/min or > 100/min)	17 [48.6]
Crackles	16 [45.7]
Intercostal retractions	12 [34.3]
Laboratory findings (median [IQR])	
Leukocyte count ($\times 10^9$ /l)	10.9 [7.7-17.5]
CRP (mg/l)	88 [44-176]
Bacterial super infection (n = [%])	
Respiratory culture positive	8 [22.9]
Blood culture positive	6 [17.1]
Mechanical ventilation (n = [%])	
None	1 [2.9]
Non-invasive	25 [71.4]
Invasive	22 [62.9]
PaO ₂ /FiO ₂ on admission (median [IQR])	219 [83-285]

* Fever = temperature $\geq 38.5^\circ\text{C}$

Hypotension/hypertension = below 90/60 or above 160/95

Data are presented as median \pm interquartile range (IQR) or as frequencies (percentages)

patients of 133 (see also *table 1*). Only one patient died after he was discharged from the ICU. Three months after completion of the study, the remaining 24 patients were still alive. Only two patients were re-admitted to the ICU within the study period.

Survivors vs. non-survivors

Differences between survivors and non-survivors are shown in *table 4*. There were no significant differences between survivors and non-survivors. Mortality was not related to vaccination status. Patients who died were more likely to have higher severity of illness at presentation: APACHE II score, SAPS II score and APACHE IV mortality rate were higher. However, these differences were not statistically significant. The rate of mechanical ventilation was equal in both groups, but the duration of ventilation was longer in the survivors in comparison with the non-survivors. This difference was also not statistically significant.

Discussion

This retrospective, observational multicentre cohort study identified all patients with confirmed influenza A or B virus infection admitted to two Dutch ICUs during the flu epidemic

Table 3. Outcome

	All (n = 35)
Duration mechanical ventilation (in hours) (median [IQR])	55 [24-155]
Use of vasopressors during admission (n = [%])	22 [62.9]
Length of stay in ICU (in days) (median [IQR])	4.18 [1.76-9.32]
Length of stay in hospital (in days) (median [IQR])	12.57 [5.40-20.71]
Mortality (n = [%])	
In ICU	10 [28.6]
In hospital	1 [2.9]
3-month mortality	0 [0.0]
Re-admission (n = [%])	2 [5.7]

Data are presented as median \pm interquartile range (IQR) or as frequencies (percentages)

Table 4. Survivors vs. non-survivors

	Survivors (n = 25)	Non-survivors (n = 10)	P value
Gender, (male/female)	14/11	6/4	0.84
Age (median [IQR])	68.0 [54-79]	71.5 [62-78.8]	0.76
Positive vaccination status (%)	80.0	70.0	0.57
Comorbidity (n = [%])			
COPD	60.0	50.0	0.61
Disease severity (median [IQR])			
SAPS II score	41 [35-45]	46 [42-75.8]	0.08
Apache II score	18 [16-23]	24.5 [18-34.8]	0.08
Apache IV score	63 [51-75]	68.5 [52.3-117.5]	0.48
Apache IV mortality rate	0.213 [0.114-0.281]	0.280 [0.151-0.637]	0.19
PSI score	127 [99-148]	133 [119-151]	0.42
CURB-65 score	2 [1-3]	2 [1-2]	0.91
Mechanical ventilation (n = [%])			
None	4.0	0.0	0.33
Non-invasive	72.0	70.0	0.91
Invasive	60.0	70.0	0.59
PaO ₂ /FiO ₂ on admission (median [IQR])	192 [76-254]	244 [150-300]	0.18
Duration mechanical ventilation (in hours) (median [IQR])	62 [42-206]	45 [20-53]	0.18
Use of vasopressors during admission (n = [%])	68.0	90.0	0.12
Length of stay in ICU (in days) (median [IQR])	5.13 [2.81-9.41]	1.96 [1.53-3.12]	0.10

Data are presented as median \pm interquartile range (IQR) or as frequencies (percentages)

P-value < 0.05 was considered to be statistically significant

of the winter of 2012-2013. This flu epidemic (lasting 18 weeks) was much longer than any other flu season in the last 20 years. Our analysis shows that the majority of the patients admitted to the ICU were over the age of 65 years and had COPD and/or a bacterial superinfection at the time of admission.

Mean ICU mortality was high, as predicted by the SAPS II, APACHE II and PSI score. To our knowledge this is one of the first European studies that has described the clinical profile and outcomes of patients admitted to the ICU during the epidemic flu season in the winter of 2012-2013. Like other flu seasons (except the Mexican flu season in 2009) especially older patients were affected.³ Despite the fact that 77.1% of the patients were vaccinated, nearly one-third (31.4%) of the 111 PCR analyses were positive for influenza A or B. Vaccination status was not associated with mortality.

As in the United States, the influenza A virus predominated from the beginning of the epidemic until the start of February 2013 (week 5), while influenza B predominated from week 6 of 2013 until the end of the epidemic.⁴ We noticed that during this flu season the prevalence of COPD in ICU patients was high, with pneumonia and exacerbation of COPD as main causes of ICU admission. Seven patients (20%), all without COPD, were septic or in shock at the time of admission. Three of them (43%) had a PaO₂ to FiO₂ ratio below 27kPa, which is an indicator for ARDS. None of the people who had COPD had a PaO₂/FiO₂ below 27 kPa. So, having COPD was not necessarily associated with a poor prognosis of the disease. Over one-third of all cases had a bacterial superinfection, with *Staphylococcus aureus* and *Streptococcus pyogenes* as most common pathogens. Only three patients (25%) with a bacterial superinfection died. The other seven patients who passed away during the study died of other causes. This corresponds to the study of Rice *et al.*⁵ who described that an infection with influenza A/B and the resulting host response can also cause severe respiratory failure, shock and multi-organ failure without a bacterial infection. Patients who survived were ventilated for a longer period than the non-survivors. This could be explained by the fact that the non-survivors were admitted to the ICU for only 1.96 days [IQR: 1.52-3.12], compared with a median of 5.13 days [IQR: 2.81-9.41] in the survivor group. The median duration of ventilation in this group was 2.29 days [IQR: 1.0-6.46]; most of the non-survivors were already dead at that time. The SAPS II, APACHE II and PSI score seemed to be useful for predicting mortality in influenza A or B positive patients admitted to our ICU. The median CURB-65 score was 2.0 [IQR: 1.0-2.5], which corresponds to a mortality of 12%. The mortality rate in our study was more than twice as high, so the CURB-65 was not a good predictor of mortality in our study population. In our study the use of vasopressors during admission was relatively high (62.9%). At admission a small percentage of the patients had hypotension. So, there were probably several factors during admission that lowered the blood pressure and/or a higher median blood pressure was pursued.

There are several limitations to our study. First, our sample size was small, so we were not able to perform a multivariate analysis that would more accurately identify factors that could predict outcome and reason for ICU admission. In addition,

the data were collected by means of electronic and paper case report forms. Accordingly, some patients had missing data. We made no assumptions regarding missing data; however, all proportions were calculated as percentages of the patients with available data.

Conclusion

Compared with other seasons, the flu season of 2012-2013 was unusually long and many patients were affected. ICU admission was associated with an age over 65 years, the presence of COPD and/or a bacterial superinfection. Mean ICU mortality was 28.6%, which corresponds to the measured SAPS II, APACHE II and PSI score. No significant differences were found between survivors and non-survivors with respect to disease severity, positive vaccination status, comorbidities and duration of ventilation.

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