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Seasonal influenza in octogenarians and nonagenarians admitted to a general hospital: epidemiology, clinical presentation and prognostic factors

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ABSTRACT

Background. Seasonal influenza is responsible for high annual morbidity and mortality worldwide, especially in elderly patients. The aim of the study was to analyse the epidemiological, clinical and prognostic features of influenza in octogenarians and nonagenarians admitted to a general hospital, as well as risk factors associated with mortality.

Methods. Retrospective, cross-sectional, descriptive study in patients admitted and diagnosed with influenza by molecular biology in the General University Hospital of Alicante from 1 January to 31 April 2015.

Results. A total of 219 patients were diagnosed with influenza in the study period: 55 (25.1%) were ≤64 years-old; 77 (35.2%) were aged 65–79; 67 (30.6%) were aged 80–89 years; and 20 (9.1%) were aged ≥90 years. Most flu episodes were caused by influenza A (n=181, 82.6%). Patients aged 80 years or older had lower glomerular filtration rate (mean: 49.7 mL/min vs. 62.2 mL/min; p=0.006), a greater need for non-invasive mechanical ventilation (22% vs 9.3%; p=0.02), greater co-morbidity due to cardiac insufficiency (40.5% vs. 16.4%; p<0.001) and chronic renal disease (32.9 vs. 20%, p=0.03), and greater mortality (19% vs. 2.9%; p<0.001). In a multivariate analysis, mortality was higher in those aged 80 or over (adjusted odds ratio [ORa] 9.2, 95% confidence interval [CI] 1.65–51.1), those who had acquired the flu in a long-term care facility (ORa 11.9, 95% CI 1.06–134), and those with hyperlactataemia (ORa 1.89, 95% CI 1.20–3.00).

Conclusions. Seasonal influenza is a serious problem leading to elevated mortality in octogenarian and nonagenarian patients admitted to a general hospital.

Key words: Human influenza; Influenza A virus; Aged care; Frail elderly; Geriatric care

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Gripe estacional en octogenarios y nonagenarios ingresados en un hospital general: epidemiología, clínica y factores pronósticos

RESUMEN

Introducción. La gripe epidémica estacional es responsable de una elevada morbi-mortalidad cada año en el mundo especialmente en pacientes de edad avanzada. El objetivo del estudio fue presentar las características epidemiológicas, clínicas y pronósticas de la gripe estacional en octogenarios y nonagenarios ingresados en un hospital general y analizar los factores asociados con la mortalidad.

Material y métodos. Estudio descriptivo transversal retrospectivo de los pacientes ingresados con gripe diagnosticados por biología molecular en el Hospital General Universitario de Alicante desde el 1 de enero del 2015 hasta 31 de abril del 2015.

Resultados. En el periodo de estudio fueron diagnosticados 219 pacientes, de ellos 55 (25,1%) eran ≤64 años, 77 (35,2%) adultos de entre 65 y 79 años, 67 (30,6%) entre 80-89 años y 20 (9,1%) ≥90 años. La mayoría de los episodios fueron gripe causada por influenza A (n=181; 82,6%). Los pacientes ≥ 80 años tenían unos valores medios de un filtrado glomerular inferior (media: 49,7 mL/min vs. 62.2 mL/min; p=0,006), mayor requerimiento de ventilación mecánica no invasiva (22% vs 9,3%; p=0,02), una mayor comorbilidad por insuficiencia cardiaca (40,5% vs. 16,4%p<0,001) y enfermedad renal crónica (32,9 vs. 20%, p=0,03), así como mayor mortalidad (19% vs. 2,9%; p<0,001). En el análisis multivariado, la mortalidad fue superior en los mayores de 80 años (odds ratio ajustada [ORa]: 9,2, intervalo de confianza [IC] del 95%: 1,65-51,1), con adquisición de la gripe en un centro socio sanitarios (ORa: 11,9, IC 95%: 1,06-134) y la hiperlactacidemia (ORa: 1,89, IC 95%: 1,20-3,00).

Conclusiones. La gripe es un grave problema con elevada mortalidad en pacientes octogenarios y nonagenarios ingresados en un hospital general.

Palabra clave: Gripe, virus de gripe A; cuidados del anciano; paciente frágil; paciente geriátrico.

INTRODUCTION

Influenza is a disease of the respiratory tract, caused by *Orthomyxovirus* types A or B, and it affects people of all ages. Influenza has a seasonal form, appearing each autumn and winter in countries of temperate climate in both hemispheres. The different clinical expression of influenza is related to prior exposure, natural or vaccine-induced, to antigens of the influenza virus[1,2]. In addition, a pandemic flu appears more rarely, about every 40 years, and it is associated with higher morbidity and mortality. The last pandemic was influenza A subtype H1N1 in 2009[1].

Most people infected with the influenza virus exhibit self-limited, uncomplicated, acute febrile respiratory symptoms or are asymptomatic. However, severe disease and complications due to infection, including hospitalisation and death, may occur in the elderly[3], in children, in people with underlying medical conditions (including pulmonary and cardiac disease, diabetes, and immunosuppression), and in some otherwise healthy people[2]. Seasonal influenza is a serious infection, and frequently it is complicated with viral or bacterial pneumonia and other bacterial infections[2–4].

The geriatric population, and especially those aged 80 or older, are among the patients most affected by seasonal influenza and those who suffer the greatest mortality and serious complications related to it[2,5–7]. In recent years, there have been numerous scientific contributions related to the pandemic influenza A H1N1[1,3,4]; however, no Spanish studies have been published on the relevance of seasonal influenza to hospital admissions in the advanced geriatric population.

The aim of our study was to analyse the epidemiological, clinical and prognostic features of influenza in octogenarians and nonagenarians admitted to a general hospital and risk factors associated with mortality.

MATERIAL AND METHODS

A retrospective, cross-sectional, descriptive study was carried out in patients with influenza admitted to the General University Hospital of Alicante, from 1 January to 31 April 2015. This centre is a tertiary hospital covering an area with 245,000 inhabitants. It has 765 beds and offers services of all medical and surgical specialties. The health department also has a long-term care facility that admits patients with medical problems requiring longer stays.

We selected all patients admitted to hospital due to influenza virus using data collected from the Minimum Basic Data Set (MBDS) database. All patients had to be diagnosed from real-time polymerase chain reaction (qPCR) samples obtained by nasal lavage with the GeneXpert test, using the Xpert Flu® and Xpert Flu/RSV XC® (RS Cepheid) assays.

Nasal lavage was performed in all patients suspected of having influenza. Patients were placed in mandatory isolation until the microbiological results were available; confirmed cases remained in isolation, while those testing negative were de-isolated. All patients with a positive result received oral treatment with oseltamivir, with dosage varying according to their weight and renal function.

We reviewed patients' clinical records, collecting data on the following variables: age, sex, place of influenza acquisition, basic analytical and biochemical parameters, co-morbidities, number of co-morbidities, complications during hospital stay, treatment used, need for non-invasive mechanical ventilation (NIMV), virus type of the infecting influenza, clinical evolution, ward of hospitalisation and length of hospital stay.

Statistical analysis. The variables were exported from the MBDS database in the form of a spreadsheet and completed from clinical records, and they were then analysed using SPSS Statistics software, version 22 (IBM Corporation). The qualitative variables are presented as a number and percentage, and the quantitative variable as a mean and standard deviation (SD). The differences between episodes of influenza in patients aged ≥80 and <80 and those related to clinical evolution were compared. Differences in qualitative variables were studied

Table 1 Distribution of influenza cases by month, sex, and age group.

	Total cases of influenza	Total admitted	%	OR (95% CI)
Total	219	9,650	2.3	
Month				
January	45	2,411	1.9	1
February	128	2,476	5.2	2.9 (2.0–4.0)
March	41	2,452	1.7	0.9 (5.6–1.4)
April	4	2,221	0.2	0.09 (0.03–0.3)
Sex				
Male	101	4,641	2.2	1
Female	118	4,919	2.4	1.1 (0.4–1.4)
Age group				
≤ 64 years	55	6,286	0.9	1
65–79 years	77	2,555	3.0	3.5 (2.5–5.0)
> 80 years	87	1,768	4.9	5.9 (4.1–8.2)

OR: odds ratio; CI: confidence interval.

Table 2 **Epidemiologic characteristics of influenza in octogenarians and nonagenarians.**

	> 80 years (total=79) N (%)	< 80 years (total =140) N (%)	P value
Sex			0.07
Male	30 (38)	71 (50.7)	
Female	49 (62)	69 (49.3)	
Place of acquisition			
Community	59 (74.7)	109 (77.9)	0.8
Long-term care facility	6 (7.6)	3 (2.1)	0.6
Nosocomial	14 (17.7)	28 (20)	0.8
Ward of admittance			
Intensive care	3 (3.8)	8 (5.7)	0.5
Analytical and biochemical parameters			
Haemoglobin (g/L), mean ± SD	11.9 ± 1.9	12.5 ± 2.3	0.05
Leucocytes ($x10^9$/L), mean ± SD	10.3 ±12.4	8.2 ± 4.5	0.06
Neutrophils ($x10^9$/L), mean ± SD	7.0 ± 4.0	6.3 ± 4.1	0.2
CRP (mg/dL), mean ± SD	8.6 ± 8.3	7.9 ± 9.2	0.6
Creatinine (mg/dL), mean ± SD	1.5 ± 1.4	1.5 ± 1.8	0.2
Urea (mg/dL), mean ± SD	65 ± 35.9	53.6 ± 37.5	0.9
Glomerular filtration (mL/min), mean ± SD	49.7 ± 22.7	62.2 ± 30.9	0.006
pH, mean ± SD (N=164)	7.4 ± 0.8	7.4 ± 0.7	0.7
Lactate (mmol/L), mean ± SD (N=164)	2.1 ± 0.8	2.2 ±1.5	0.3
Type of influenza			0.9
Influenza A*	64 (81.0)	117 (80)	
Influenza B	15 (19.0)	23 (20)	
Treatment			
NIMV	18 (22.8)	13 (9.3)	0.02
Antibiotic treatment	51 (64.6)	81 (67.9)	0.2
Steroid treatment	39 (40.6)	57 (59.3)	0.3
Forms of presentation			
Pneumonia	16 (20.3)	16 (11.4)	0.07
Co-morbidities			
Diabetes mellitus	19/79 (24.1)	27/140 (19.3)	0.4
Hypertension	34/79 (43.0)	58/140 (41)	0.8
Cardiac insufficiency	32/79 (40.5)	23/140 (16.4)	<0.001
Chronic renal diseases	26/79 (32.9)	28/140 (20)	0.03
Outcome			
Mortality	15 (19)	4(2.9)	<0.001
Length of hospital stay, mean ± SD	10.4 ± 11.2	9.9 ± 9.3	0.7

CRP: C reactive protein; NIMV: non-invasive mechanical ventilation; SD: standard deviation.

*** includes Influenza A H1N1**

using the Chi-squared test, or alternatively Fisher's exact test when the number of expected cases was under five in one of the cells. Quantitative variables were analysed according to the Student's t-test if they followed a normal distribution; otherwise the U Mann Whitney test was used. Variables presenting a p value < 0.05 in the univariate study were included in the binary logistic regression multivariate analysis. The association was measured according to the adjusted odds ratio (ORa) and its 95% confidence interval (CI). The Institutional Ethics Committee of Hospital General Universitario de Alicante approved the study protocol.

RESULTS

During the study period, 9,560 patients over 15 years old were admitted, and 219 (2.3%) had a diagnosis of influenza by molecular biology. The risk of admission due to influenza was higher in February than in January (OR 2.9, 95% CI 2.0–4.0) (table 1). Of the 219 patients with influenza, 55 (25.1%) were ≤ 64 years old, 77 (35.2%) were aged between 65–79 years old, 67 (30.6%) were aged 80–89, and 20 (9.1%) were aged ≥ 90. Compared to patients aged ≤ 64 years, the risk of admission due to influenza was greater in adults aged 65–79 years (OR 3.5, 95% CI 2.5–5.0) and especially in those aged ≥ 80 years (OR 5.9, 95% CI 4.1–8.2) (table 1). Most patients with influenza (n=156, 71.2%) were admitted to the General Internal Medicine, Infectious Diseases, or Respiratory Medicine Departments, and only 11 (5.0%) patients were admitted into the Intensive Care Unit. Regarding the place of infection by influenza, 76.7% (n=168) of cases were community-acquired, 4.1% (n=9) were associated with long-term care facilities, and 19.2% (n=42) were nosocomial infections. Influenza virus type A produced most of the influenza cases (n=175, 79.9%), while influenza virus type B virus was identified in 38 (17.4%) patients, and pandemic

Table 3 **Bivariate analysis of the risk factors for mortality associated with infection from the influenza virus.**

	Dead (n=19) N (%)	Not dead (n=200) N (%)	OR (95% CI)	P value
Sex				0.7
Male	8 (42.1)	93 (46.5)	1	
Female	11 (57.9)	107 (53.5)	1.19 (0.46–3.09)	
Age				<0.001
< 80 years	4 (21.1)	136 (68.0)	1	
≥ 80 years	15 (78.9)	64 (32.0)	7.96 (2.54–24.9)	
Place of acquisition				
Community	11 (57.9)	157 (78.5)	0.37 (1.43–0.99)	0.04
Long-term care facility	3 (15.8)	6 (3.0)	6.06 (1.38–26.5)	0.007
Nosocomial	5 (26.3)	37 (18.5)	1.57 (0.53–4.64)	0.4
Co-morbidities				
Diabetes mellitus	4 (21.1)	42 (21)	0.99 (0.31–3.16)	0.9
Hypertension	9 (47.4)	83 (41.5)	1.26 (0.49–3.26)	0.6
Chronic cardiac insufficiency	8 (42.1)	47 (23.5)	2.36 (0.90–6.23)	0.07
Anaemia	4 (21.1)	38 (19)	1.13 (0.35–3.62)	0.8
Chronic renal disease	4 (21.1)	50 (25.0)	0.80 (0.25–2.52)	0.7
Chronic pulmonary disease	2 (10.5)	17 (8.5)	1.26 (0.27–5.95)	0.7
Haemogram and biochemistry				
Leucocytes (x10^9/L), mean ± SD	10.92 ± 5.3	8.8 ± 8.5	1.09 (0.92–1.32)	0.36
Neutrophils (x10^9/L), mean ± SD	8.7 ± 4.7	6.4 ±4.0	1.11 (1.01–1.21)	0.03
CRP (mg/dL), mean ± SD	14.6 ± 12.7	7.6 ± 8.2	1.06 (1.02–1.11)	0.002
PH, mean ± SD (N=164)	7.3 ± 0.10	7.41 ±0.8	0.007 (0.0–2.33)	0.09
Lactate (mmol/L), mean ± SD (N=164)	3.1 ± 3.0	2.1 ±0.9	1.49 (1.05–2.14)	0.02
Creatinine (mg/dL), mean ± SD	1.44 ± 0.81	1.56 ± 1.7	0.93 (0.65–1.32)	0.7
Urea (mg/dL), mean ± SD	75.1 ± 34.8	56.1 ± 37.2	1.01 (1.00–1.02)	0.03
Glomerular filtration (mL/min), mean ± SD	45.1 ± 19.9	58.9 ± 29.2	0.98 (0.96–1.00)	0.08
Type of influenza				0.8
Influenza A	16 (84.2)	165 (82.5)	1	
Influenza B	3 (15.8)	35 (17.5)	1.13 (0.31–4.09)	
Requirements and complications				
NIMV	7 (36.8)	24 (12)	4.27 (1.5–11.9)	0.003
Pneumonia	8 (42.1)	24 (120)	5.33 (1.9–14.5)	0.001

CRP: C reactive protein; NIMV: non-invasive mechanical ventilation; SD: standard deviation.

subtype H1N1 was found in 6 (2.7%) cases.

The clinico-epidemiological characteristics of influenza episodes in octogenarians and nonagenarians are presented in table 2. There were some statistically significant differences between patients under 80 and those aged 80 years or older. The older patients had a lower glomerular filtration rate (p=0.006), a greater need for NIMV (p=0.02), and higher mortality (p<0.001). Pneumonia was also more common in this group, but the difference was not statistically significant (20.3% vs. 11.4%; p=0.07). The mean length of hospital stay was 10.4 (± 11.2) days in patients aged 80 or older, very similar to that registered in younger patients.

Nineteen (8.7%) patients died: 2 (3.6%) of the 55 patients aged 64 or under, 2 (2.6%) of the 77 patients aged 65 to 79, and 15 (17.2%) of the 87 patients aged 80 or older (p=0.001). Table 3 shows the factors related to mortality. In the multivariate analysis, mortality was higher among those aged 80 or older (ORa 9.2, 95% CI 1.65–51.35), those who had acquired influenza in a long-term care facility (ORa 11.9, 95% CI 1.06–134), and those with hyperlactataemia (ORa 1.89, 95% CI 1.20–3.00) (table 4).

DISCUSSION

In our study, the risk of hospitalisation for influenza was higher in geriatric patients aged 65 years or older and particularly in those aged 80 or older. During the study period, mortality in patients with influenza was positively associated with advanced age (≥80 years), presence of co-morbidities, infection by influenza virus in a long-term care facility and diagnosis of lactic acidosis during the course of the disease.

The most frequently observed co-morbidities in our patients were: diabetes mellitus, hypertension, chronic renal disease and cardiac in-

Table 4 **Multivariate analysis of risk factors for mortality.**

Variables	Adjusted OR (95% CI)	P value
Lactate (mmol/L)	1.89 (1.20–3.00)	0.006
Age ≥80 years	9.2 (1.65–51.35)	0.01
Acquisition in long-term care facility	11.9 (1.06–134)	0.04
Pneumonia	3.7 (0.85–16.1)	0.08
CRP (mg/dL),	1.04 (0.97–1.11)	0.2
Community acquisition	0.45 (0.09–2.25)	0.3
Neutrophils (x10^9/L)	1.05 (0.98–1.22)	0.5
NIMV	1.89 (0.45–5.61)	0.4
Urea (mg/dL)	1.0 (0.97–1.02)	0.9

CI: confidence interval; CRP: C reactive protein; NIMV: non-invasive mechanical ventilation.

sufficiency. People at high risk of complications from influenza include patients with chronic obstructive pulmonary disease, cardiovascular disease, immunosuppressive disorders, chronic renal dysfunction, cancer, cognitive dysfunction, and diabetes mellitus, among other disorders, as well as residents of any age in long-term care institutions. These conditions are quite frequent in elderly people, who often require hospital admission and antiviral treatment[2].

Influenza is associated with heart failure and other cardiovascular disease, as found by a recent systematic review and meta-analysis[8]. In our study, the prevalence of heart failure in patients admitted with influenza was higher, but it was more common in people aged 80 or older. Moreover, in our study, renal insufficiency as evaluated by estimated glomerular filtration rate was lower in patients aged ≥ 80 years than in younger patients. In addition to advanced age, obesity and pro-inflammatory mediators have also been associated with kidney failure in patients with influenza[9]; however, we did not analyse these features in our study. Pneumonia is a severe complication in patients aged over 65 years who are hospitalised with influenza[10]. In our study, this pathology was a more frequent complication in octogenarians and nonagenarians with influenza compared to younger patients, but the difference did not reach statistical significance.

The World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) recommend neuraminidase inhibitors such as oseltamivir and zanamivir as the first-line antiviral drugs for patients infected with influenza A and B[11,12]. Current guidelines recommend antiviral treatment with oseltamivir within 48 h of symptom onset in all patients admitted with laboratory confirmed or highly suspected influenza[2]. In our hospital, we followed these recommendations during the study period. All of patients received the treatment with oseltamivir 12 hours previously laboratory confirmed diagnosis or during the first 8 hours after that.

Seasonal influenza is a serious, potentially fatal entity[13]. Indeed, in a document published by the prestigious Statens Serum Institut in Copenhagen, the excess all-cause mortality registered between December 2014 and February 2015 was attributed to a rise in the number of influenza H3N2 cases in that time period[14]. It is well known that mortality due to the seasonal influenza virus is more frequent in those aged 65 or older[5,6,15], but in our study, we have demonstrated that mortality is particularly high in patients aged 80 years or older. Population ageing is a social reality, and we have shown that the advanced geriatric population (aged ≥80) is at increased risk of dying due to influenza.

The severity of influenza in chronically ill and elderly populations (especially octogenarians and nonagenarians) strongly advises adherence to recommendations on influenza vaccination[2,15]. Different epidemiological studies have demonstrated that the influenza vaccine reduces hospitalisations and mortality related to that cause[16,17]. In our health department, influenza vaccination is free and easily accessible in primary healthcare centres and in hospital. However, during the 2014–15 influenza season, antigenic drift caused most of the influenza A (H3N2) viruses in circulation to be different from the influenza A (H3N2) component of the 2014–15 northern hemisphere seasonal vaccines, resulting in a reduction in vaccine effectiveness[18,19]. The lack of protection from the flu vaccine during the study period probably had a negative influence on our patients' outcomes.

The limitations of this study include the fact that we only have information on patients admitted to hospital with influenza, not on the results for outpatients. Among the infected patients who do not require hospitalisation, mortality is lower.

Influenza in the advanced geriatric population is a serious infection. Patients over 80 have more cardiovascular disease and poorer renal function than younger patients with influenza. Advanced age, acquisition of the infection in a long-term care facility, and hyperlactaemia are associated with poor outcomes for seasonal influenza infection in admitted patients. Vaccine programmes, chemoprophylaxis during outbreaks in hospital or long-term care settings, antiviral agents, and treatment of co-morbidities can improve prognosis of elderly people with influenza.

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CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest

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