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ORIGINAL ARTICLE

Severe pandemic (H1N1)v influenza A infection: Report on the first deaths in Spain

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ABSTRACT

Background and objective: **The impact of pandemic influenza A (H1N1)v infection is still unknown but it is associated with a high case-fatality rate.**

Methods: **This was a prospective, observational, multicentre study conducted in 144 Spanish intensive care units. Demographic and clinical data were reviewed for all cases of pandemic influenza A (H1N1)v infection reported from 23 June 2009 through 11 February 2010 and confirmed by reverse transcriptase PCR assay.**

Results: **Out of 872 cases reported by statewide surveillance, data for the first 131 deceased patients were analysed. Thirty-seven patients (28.2%) died within the first 14 days. The median age of these patients was 46 years (interquartile range 35–58) and 60.3% were male. Twenty-eight patients (21.4%) did not present with any comorbidities on admission. Forty-six per cent of patients were reported to be obese and 22 (16.8%) had COPD. The vast majority of the patients (72.5%) had viral pneumonia; 95.4% of these had bilateral patchy alveolar opacities (predominantly basal), affecting three or four quadrants. One hundred and fifteen patients (87.8%) developed multi-organ dysfunction syndrome. Ninety-seven patients (74%) required vasopressor drugs, 37 (27.2%) received renal replacement therapy, and 47 (35.1%) received intravenous corticosteroids on admission to the intensive care unit. Only 68 patients (51.9%) received empirical antiviral treatment.**

Conclusions: **One-third of patients with pandemic influenza A (H1N1)v infection died within the first two weeks and these were young patients, with rapidly progressive viral pneumonia as the primary cause of admission. Obese patients were at high risk but one in four patients did not present with any risk factors on admission. Only half the patients received empirical antiviral therapy and this was administered late.**

SUMMARY AT A GLANCE

The impact of pandemic (H1N1)v influenza A infection is still unknown but it is associated with a high case-fatality rate. This prospective, observational, multicentre study conducted in 144 Spanish intensive care units, summarizes the clinical characteristics of the first 131 patients who died during the initial wave of infection.

Key words: clinical epidemiology, critical care medicine, H1N1, mortality, pneumonia.

INTRODUCTION

Pandemic influenza A (H1N1)v infection has been spreading across Europe since the first cases were reported over the summer of 2009. The European Centre for Disease Prevention and Control (ECDC) reported that up to 15 February 2010, 2678 deaths had occurred across Europe[1]; however, the impact of pandemic influenza A (H1N1)v infection is still unknown.

Reports from other continents indicate that critical illness caused by pandemic influenza A (H1N1)v infection is associated with a high case-fatality rate. We previously reported that the first 32 cases of severe respiratory failure caused by pandemic influenza A

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(H1N1)v infection in Europe had a 25% mortality rate during summer.[2] The present report summarizes the clinical details of the first 131 patients who died after admission to intensive care units (ICU) during the initial winter (2009–2010) wave of pandemic influenza A (H1N1)v infection in Spain.

METHODS

The sources of the data for this study have been described in detail previously.[2] Consecutive initial notifications of cases of influenza A (H1N1)v infection up to 15 February 2010 were eligible for inclusion in the study. Children under 15 years of age were not enrolled in this registry. Patient information was anonymized and informed consent was waived due to the observational nature of the study, and the fact that it was performed as part of an emergency public health response. All tests and procedures were ordered by the attending physicians. The study was approved by the ethics board of Joan XXIII University Hospital, Tarragona, Spain.

Nasopharyngeal swab specimens were collected at admission and respiratory secretions were also obtained from intubated patients. RT-PCR testing was performed in accordance with the published Centers for Disease Control guidelines.[3] H1N1 testing was performed at each institution or, when testing was not available, at a central reference laboratory. A 'confirmed case' was defined as an acute respiratory illness with laboratory-confirmed pandemic influenza A (H1N1)v infection, with viral infection confirmed by real-time RT-PCR or viral culture.[4] Only 'confirmed cases' were included in the present analysis.

The definition of community-acquired pneumonia was based on the current American Thoracic Society and Infectious Disease Society of America guidelines.[5] Primary viral pneumonia was defined as presentations during the acute phase of influenza virus illness, with acute respiratory distress and unequivocal alveolar opacification involving two or more lobes, and with negative respiratory and blood bacterial cultures. Co-infection was considered in patients with confirmed pandemic influenza A (H1N1)v infection, who showed recurrence of fever, increased coughing and production of purulent sputum, as well as positive results for pathogen isolation in respiratory or blood cultures.[6] BAL was not systematically performed because of the high risk of generating aerosols. Respiratory cultures were performed on tracheal aspirates obtained immediately after intubation. Acute renal failure was defined as the need for renal replacement therapy, according to the guidelines of the International Consensus Conference.[7]

The criteria for admission to ICU and treatment decisions for all patients, including determination of the need for intubation and the types of antibiotic and antiviral therapy administered, were not standardized and were made by the attending physician. The following information was recorded: demographic details, comorbidities, time of onset of illness and hospital admission, time to first dose of antiviral therapy, microbiological findings and CXR findings at admission to ICU. Empirical antiviral therapy was divided into four equal periods for the purpose of reporting implementation during the study. Intubation and mechanical ventilation requirements, adverse events during the ICU stay, for example, need for vasopressor drugs or renal replacement therapy, and laboratory findings at admission to ICU were also recorded. To assess the severity of illness, the Acute Physiology and Chronic Health Evaluation (APACHE) II score[8] was determined for all patients, within 24 h of admission to ICU. In addition, organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system.[9]

Statistical analysis

Discrete variables are expressed as counts (percentages) and continuous variables as means ± SD or medians with 25th to 75th percentiles (interquartile range, IQR). Survival analysis was performed using the Kaplan–Meier distribution. Statistical analyses were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Data are reported for the first 140 adult patients who died due to pandemic influenza A (H1N1)v infection after admission to ICUs with severe respiratory failure, in 144 hospitals in Spain. Nine cases were excluded due to missing data. Therefore, data for 131 patients were included in the final analysis. In eight patients (6.1%) infection was due to nosocomial transmission, two of these being health-care workers. Thirty-seven patients (28.2%) died within the first 14 days and 98 patients (74.8%) died within 28 days of ICU admission (Fig. 1). The median hospital stay was 13 days (IQR 6.5–22).

Pandemic influenza A (H1N1) virus infection was confirmed in all patients by real-time PCR. The median time from onset of symptoms to a confirmed

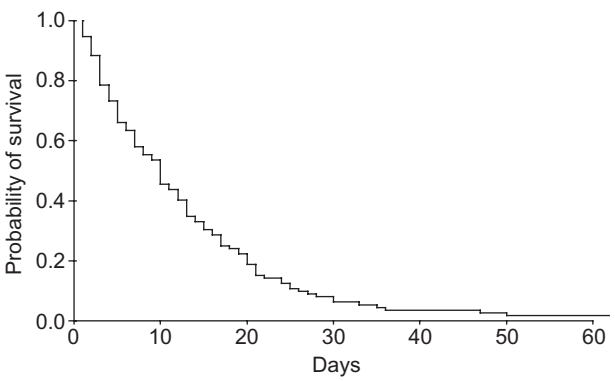

Figure 1 Cumulative survival of the 131 patients admitted to intensive care units with pandemic influenza A (H1N1)v infection (censored at 60 days).

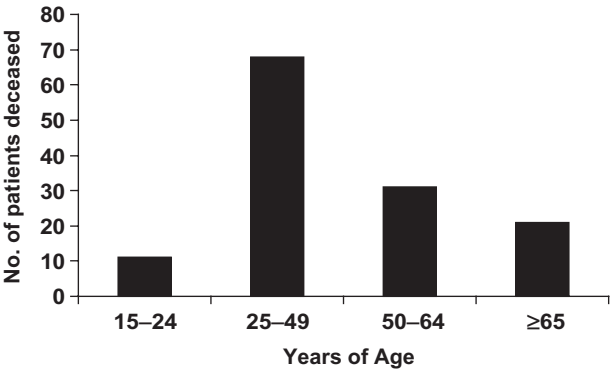

Figure 2 Number of patients with pandemic influenza A (H1N1)v infection who died after admission to the intensive care unit, according to age group.

positive real-time PCR test was 2 days (IQR 1–4). Initial PCR testing for pandemic influenza A (H1N1)v virus at ICU admission was negative in four patients (3.1%). These patients were later confirmed to be infected with the virus through testing of tracheal secretions.

The median age of the patients was 46 years (IQR 35–58). The highest number of ICU deaths occurred among patients between 25 and 49 years of age (Fig. 2). Seventy-nine patients (60.3%) were male. The median number of comorbidities was two (IQR 1–2). Sixty-one patients (46.6%) were reported to be obese (BMI > 30 in 25 patients (19.1%) and BMI > 40 in 36 patients (27.5%)) and 22 patients (16.8%) had COPD. In addition, six pregnant women (4.6%) died. Twenty-eight patients (21.4%) did not present with any comorbidities on admission. Additional demographic details and data on risk factors and types of critical illness among patients with pandemic influenza A (H1N1)v infection are presented in Table 1.

The median time from onset of symptoms to hospital admission was 4 days (IQR 2–5) and from hospitalization to ICU admission was 1 day (IQR 1–3). The vast majority of patients (95, 72.5%) had viral pneumonia (Table 2); most of these patients (95.4%) had bilateral patchy alveolar opacities (predominantly basal), affecting three or four quadrants. Co-infections occurred in 24 patients (18.3%), seven patients (5.3%) had fulminant myocarditis, four (3.1%) had exacerbations of COPD and one had hepatic failure. Table 3 shows details of the microorganisms isolated from patients with co-infections. Combination therapy was administered to 22 (91.7%) of these patients, with 12 (54.5%) receiving third-generation cephalosporins, eight (36.6%) receiving carbapenems and two (16.6%) receiving piperacillin/tazobactam.

All but three patients were mechanically ventilated, with 125 (95.4%) requiring invasive ventilation for a median of 11 days (IQR 5–17) and 45 (34.4%) of these patients requiring ventilation in the prone position. The total number of days of ventilation was 1289. Non-invasive ventilation (VIN) was implemented in 34 patients (25.9%). Thirty-one of these patients (91.2%) required further orotracheal intubation and invasive mechanical ventilation.

The mean APACHE II score was 19.2 ± 8.9 and the mean SOFA score was 8.2 ± 4.5. One hundred and fifteen patients (87.8%) developed multi-organ dysfunction syndrome. Ninety-seven patients (74%) required vasopressor drugs, 37 (27.2%) received renal replacement therapy due to acute renal failure and 47 (35.1%) received intravenous corticosteroids at ICU admission. Ventilator-associated pneumonia was

Table 1 Most common risk factors for mortality among patients with pandemic influenza A (H1N1)v infection admitted to the intensive care unit

Risk factor	Number of patients	Percentage of patients
Obesity	61	46.6
BMI > 30	25	19.1
BMI > 40	36	27.5
COPD	22	16.8
Diabetes mellitus	14	10.7
Chronic heart failure	13	9.9
Chronic renal failure	12	9.2
Asthma	11	8.4
Pregnancy	6	4.6
Neuromuscular disease	7	5.3
Autoimmune disorders	7	5.3
HIV infection	4	3.1
None	28	21.4

Table 2 Primary cause of admission for patients who died due to pandemic influenza A (H1N1)v infection

Cause of admission	Number of patients	Percentage of patients
Viral pneumonia	95	72.5
Co-infection	24	18.3
Fulminant myocarditis	7	5.3
Exacerbation of COPD	4	3.1
Fulminant hepatic failure	1	0.7

Table 3 Frequency of isolation of specific pathogens in patients with co-infections and pandemic influenza A (H1N1)v infection

Pathogen	Number of patients	Percentage of patients
Streptococcus pneumoniae	9	37.5
Aspergillus sp.	5	20.8
Pseudomonas aeruginosa	4	16.7
Streptococcus pyogenes	2	8.3
Acinetobacter baumannii	2	8.3
Staphylococcus aureus	1	4.2
Klebsiella pneumoniae	1	4.2

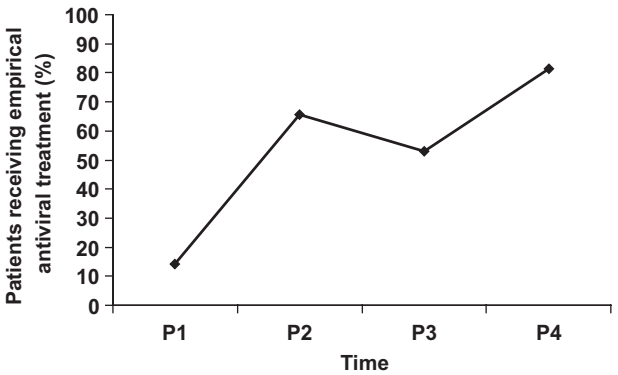

Figure 3 Percentage of patients with pandemic influenza A (H1N1)v infection who received empirical antiviral treatment over the time course of the study, divided into four equal periods. P, period.

microbiologically confirmed in 12 patients, including seven cases of *Pseudomonas aeruginosa* infection, four cases of *Acinetobacter* sp. infection and one case of *Klebsiella pneumoniae* infection.

Eighty-one patients (61.8%) had elevated LDH levels (mean 1651.6 ± 4980.4 U/L) at the time of ICU admission. Eighty-three patients (63.3%) had elevated aspartate aminotransferase levels (mean 183.4 ± 734.4 U/L), 78 (59.5%) had elevated alanine aminotransferase levels (mean 171.1 ± 758.2 U/L) and 31 (23.6%) had increased creatine kinase levels (mean 738.1 ± 662.2 U/L, range 226 to 3060). CRP levels were assessed in 48 patients (36.6%), for whom the mean value was 396 ± 527 mg/L and procalcitonin was measured in 39 patients (29.7%), for whom the mean value was 6.1 ± 20.3 ng/mL. The mean leucocyte count was of 9.36 ± 12.95 × 10^9/L and the mean platelet count was 149.57 ± 88.85 × 10^9/L. In 25 patients (19.08%), creatinine and urea were elevated at hospital admission, with mean values of 245.8 ± 107 μmol/L and 43.2 ± 12.9 mmol/L, respectively (Table 4).

Oseltamivir was administered to all patients, including higher doses of oseltamivir (up to 150 mg orally, bd) in 77 patients (58.8%). In 58 patients (85.2%) this was the initial dose. Empirical antiviral treatment was initiated in 68 patients (51.9%); however, implementation increased from 14.3% to 81.5% through the study period (Fig. 3). The estimated median time from the onset of illness to the initiation of antiviral treatment was 4 days (IQR 3–6). Zanamivir was administered as rescue therapy to only two patients (1.5%), due to the persistence of symptoms.

Table 4 Characteristics of the 131 patients who died due to pandemic influenza A (H1N1)v infection

Variable	Value
Age, years	
Mean ± SD	46.5 ± 16.1
Median (IQR)	46 (35–58)
Male gender, *n* (%)	79 (60.3)
APACHE II score, mean ± SD	19.2 ± 8.9
SOFA score, mean ± SD	8.2 ± 4.5
Days from onset of symptoms to hospital admission	
Mean ± SD	3.9 ± 2.4
Median (IQR)	4 (2–5)
Days from hospitalization to ICU admission	
Mean ± SD	2.7 ± 3.1
Median (IQR)	1 (1–3)
Days from onset of symptoms to first dose of antiviral therapy	
Mean ± SD	4.9 ± 3.6
Median (IQR)	4 (3–6)
Laboratory findings, median (IQR)	
Leucocyte count, ×10^9/L	6.8 (3–12)
Platelet count, ×10^9/L	137 (88.8–196)
Serum LDH, IU/L	780 (481.5–1133.5)
Serum creatine kinase, U/L	195 (93–514.5)
Serum creatinine (μmol/L)	79.6 (61.9–123.8)
Aspartate aminotransferase (U/L)	60 (41–118)
Alanine aminotransferase (U/L)	42.5 (24.5–101)
Mechanically ventilated on admission, *n* (%)	
Failure of NIV	31 (23.6)
Invasive ventilation	125 (95.4)
Adverse events, *n* (%)	
Vasopressor drugs	97 (74)
Haemofiltration	37 (27.2)
Refractory hypoxaemia requiring prone ventilation	45 (34.3)

APACHE, the Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; NIV, non-invasive ventilation; SOFA, Sequential Organ Failure Assessment.

DISCUSSION

This report provides details of the first 131 patients who died due to pandemic influenza A (H1N1)v infection after hospitalization in an ICU in Spain. One-third of the patients died within the first 2 weeks. The primary cause of severe pulmonary damage was rapidly progressive viral pneumonia, but only half the patients received empirical antiviral therapy, and this was administered late. The patients who died were young, and almost half were reported to be obese; however, one in four patients did not present with any risk factors on admission.

The infection was first reported in Mexico in April 2009 and several reports have been published regarding severe respiratory infections in hospitalized patients. Pérez-Padilla *et al.*[10] reported a mortality rate of 38%, while studies from Canada,[11] and Australia and New Zealand[12] indicated mortality rates of 17.3% and 14.3%, respectively. In the present cohort, 15.3% of the patients died and this report summarizes some of the important clinical findings.

Why these severe manifestations of influenza infection occurred in young adult patients during this outbreak remains an unanswered question. Pandemic

(H1N1)v influenza A infection represents a challenge due to the fact that young healthy people were affected. Some important considerations should be highlighted. First, the age-specific incidence rates were highest among adults up to 65 years of age, who represented more than 80% of the entire cohort. The present findings are in agreement with previously published reports that severe viral pneumonia affected patients who were younger than expected.[13] Second, half of the patients in the present cohort were obese; however, the potential causality of this association should be further investigated in terms of attributable mortality and utilization of hospital resources.

In addition, one in four of the patients who died did not present with any risk factor on admission. This may be explained by an abnormal immune response in these patients. We recently reported that severe pandemic (H1N1)v influenza A infection with respiratory involvement was characterized by early secretion of Th17 and Th1 cytokines that are usually associated with cell-mediated immunity.[14] Furthermore, To *et al*. recently reported immune dysregulation (excessive cytokine activation) and slower control of viral load in patients with mild compared with severe presentations.[15]

Pulmonary compromise in the present patients could be mostly explained by rapidly progressive viral hypoxaemia and bilateral alveolar infiltrates on CXR. Most patients were mechanically ventilated and despite implementation of the prone position, one in three patients subsequently died. Some reports have emphasized the importance of early recognition of hypoxaemia and management in the ICU.[16] In the present study, NIV was unsuccessful in more than 20% of patients. Recently, the European Respiratory Society and the European Society of Intensive Care Medicine published guidelines on the use of NIV in patients with pandemic (H1N1)v influenza A infection.[17] It was suggested that, as a rule, NIV is not recommended as an alternative to invasive ventilation in these patients. The implementation of NIV may be considered in order to prevent clinical worsening and the need for intubation in patients with moderate hypercapnic respiratory exacerbations, chronic lung disease or cardiogenic pulmonary oedema, but without primary viral pneumonia, multi-organ dysfunction/failure or refractory hypoxaemia.[18]

In the present study, co-infection was identified in 18.3% of the patients, whereas a recent analysis of 77 fatal cases of pandemic (H1N1)v 2009 infection indicated bacterial co-infection in 29% of patients.[19] The present findings were in agreement with that report in terms of the common bacterial pathogens causing co-infection: *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Streptococcus pyogenes*. Interestingly however, *Aspergillus* sp. was isolated from deep respiratory samples of five patients, and *Pseudomonas aeruginosa* was isolated from those of four patients.

Extrapulmonary manifestations of pandemic (H1N1)v influenza A infection have been reported to be associated with more severe presentations.[20] A striking observation in the present cohort was the seven patients who were admitted with fulminant myocarditis. The prevalence of influenza-associated fulminant myocarditis is not known because of the low index of suspicion. Bratincsák *et al*.[21] reported four children with fulminant myocarditis; therefore early detection and aggressive therapy are warranted in order to decrease mortality.

Empirical antiviral treatment was initiated in only half the patients who died. This finding was surprising, given that empirical antiviral treatment should be initiated within the first 48 h of the onset of symptoms and is recommended for all hospitalized patients admitted with suspected influenza.[22,23] Jain *et al*. reported that among 272 hospitalized patients with positive RT-PCR tests for pandemic (H1N1)v influenza A infection, those who received antiviral drugs (188 out of 200 receiving oseltamivir) within 2 days of the onset of symptoms had better outcomes.[24] Hien *et al*. reported clinical, RT-PCR and viral culture data from 292 patients with pandemic (H1N1)v influenza A infection, who commenced oseltamivir at hospital admission, and observed that antiviral treatment resulted in a rapid decline in viral shedding.[25] Nevertheless, the implementation of empirical antiviral therapy increased markedly over the period of the study due to the campaigns of the Spanish National Health System (Fig. 3).

In conclusion, the results from this study show that in patients who died due to pandemic (H1N1)v influenza A infection, rapidly progressive viral pneumonia was the primary cause of admission, and only half of these patients received empirical antiviral therapy. These observations emphasize the importance of a high index of suspicion for pandemic (H1N1)v influenza A infection, with early detection, aggressive management and concomitant use of antiviral drugs.

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