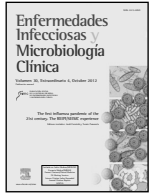




Enfermedades Infecciosas y Microbiología Clínica

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Influenza A(H1N1)pdm09-related pneumonia and other complications

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ABSTRACT

Keywords:

Influenza A(H1N1)pdm09 virus
Complication
Pneumonia
Intensive care unit
Mortality

Influenza A(H1N1)pdm09 virus infection was associated with significant morbidity, mainly among children and young adults. The majority of patients had self-limited mild-to-moderate uncomplicated disease. However, some patients developed severe illness and some died. In addition to respiratory complications, several complications due to direct and indirect effects on other body systems were associated with influenza A(H1N1)pdm09 virus infection. The main complications reported in hospitalized adults with influenza A(H1N1)pdm09 were pneumonia (primary influenza pneumonia and concomitant/secondary bacterial pneumonia), exacerbations of chronic pulmonary diseases (mainly chronic obstructive pulmonary disease and asthma), the need for intensive unit care admission (including mechanical ventilation, acute respiratory distress syndrome and septic shock), nosocomial infections and acute cardiac events. In experimentally infected animals, the level of pulmonary replication of the influenza A(H1N1)pdm09 virus was higher than that of seasonal influenza viruses. Pathological studies in autopsy specimens indicated that the influenza A(H1N1)pdm09 virus mainly targeted the lower respiratory tract, resulting in diffuse alveolar damage (edema, hyaline membranes, inflammation, and fibrosis), manifested clinically by severe acute respiratory distress syndrome with refractory hypoxemia. Influenza A(H1N1)pdm09-related pneumonia and other complications were associated with increased morbidity and mortality among hospitalized patients.

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Neumonía relacionada con la gripe A(H1N1)pdm09 y otras complicaciones

RESUMEN

Palabras clave:

Virus de la gripe A (H1N1)pdm09
Complicaciones
Neumonía
Unidad de cuidados intensivos
Mortalidad

Si bien la mayoría de los pacientes infectados por el virus de la gripe A(H1N1)pdm09 tuvieron enfermedad no complicada, autolimitada, leve a moderada, la infección se caracterizó por una morbilidad significativa, especialmente entre niños y adultos jóvenes, de forma que algunos pacientes desarrollaron una enfermedad grave y algunos murieron. La infección por virus de la gripe A(H1N1)pdm09 se asoció no sólo con complicaciones respiratorias, sino también con complicaciones debidas a los efectos directos e indirectos sobre otros sistemas del organismo. En los pacientes adultos hospitalizados las complicaciones principales fueron neumonía (neumonía primaria por gripe y neumonía bacteriana concomitante/secundaria), exacerbaciones de enfermedades pulmonares crónicas (principalmente enfermedad pulmonar obstructiva crónica y asma), necesidad para la admisión en unidad de cuidados intensivos (incluso ventilación mecánica, síndrome de dolor respiratorio agudo y shock séptico), infecciones nosocomiales y acontecimientos cardíacos agudos. En los animales de experimentación infectados con virus de la gripe A(H1N1)pdm09 el nivel de replicación del virus a nivel pulmonar era más alto que el de los virus de la gripe estacional. Los estudios anatomopatológicos de muestras de autopsia mostraron que el virus de la gripe A(H1N1)pdm09 actúa principalmente sobre el tracto respiratorio inferior, provocando lesión difusa del alveolo (edema, membranas hialinas, inflamación y fibrosis), lo que se traduce clínicamente en un síndrome de distrés respiratorio agudo grave con hipoxemia refractaria. La neumonía y otras complicaciones relacionadas con la gripe por virus A(H1N1)pdm09 se asociaron a una mayor morbilidad y mortalidad en los pacientes hospitalizados.

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Introduction

Since the 16th century, influenza pandemics have been described all over the world, at intervals ranging from 10 to 50 years and with varying degrees of severity. In April 2009, a novel influenza virus now known as influenza A(H1N1)pdm09 virus caused an outbreak of respiratory disease in Mexico¹ and spread rapidly worldwide, resulting in the first influenza pandemic of this century. Spain was the first country in Europe to report a laboratory-confirmed case of influenza A(H1N1)pdm09 virus infection.² The number of hospitalizations and deaths due to influenza A(H1N1)pdm09 increased continuously until December 2009. It was recently reported that influenza A(H1N1)pdm09 virus infection during the 2010-2011 influenza season was associated with higher morbidity than that observed during the pandemic period.^{3,4}

Children and young adults accounted for most cases of influenza A(H1N1)pdm09 virus infection. The majority of patients had self-limited, mild-to-moderate uncomplicated disease. However, some patients developed severe illness and some died. Common symptoms included cough, fever, sore throat, myalgia and headache. Some cases experienced gastrointestinal symptoms (nausea, vomiting and/or diarrhea).⁵ The major complications of influenza were those involving the lower respiratory tract, mainly pneumonia.⁶ In addition, secondary bacterial infections, rhabdomyolysis with renal failure, seizures, and worsening of underlying conditions such as cardiovascular disease were also reported.^{5,6} Influenza A(H1N1)pdm09-related pneumonia and other complications were associated with increased morbidity and mortality.

The purpose of this article is to summarize the experience of the Spanish Network for the Research in Infectious Diseases (REIPI) with regard to influenza A(H1N1)pdm09-related pneumonia and other complications. We also performed a literature review regarding complications associated with influenza A(H1N1)pdm09.

Influenza A(H1N1)pdm09-related pneumonia

The most frequent serious complications of influenza are pulmonary, and fall into four categories: primary influenza pneumonia, secondary bacterial pneumonia, pneumonia due to unusual pathogens or in immunocompromised hosts, and exacerbations of chronic pulmonary diseases.⁶ Interestingly, in experimentally infected animals, the level of pulmonary replication of the influenza A(H1N1)pdm09 virus was higher than that of seasonal influenza viruses.⁷ The frequency of complications in the REIPI cohort of hospitalized patients with influenza A(H1N1)pdm09 virus infection is detailed in Table 1.

In the REIPI cohort, 585 patients (median age 40 years) required hospitalization. Chest radiography was obtained on 542. A total of 234 patients (43.1%) had pneumonia, of whom 210 underwent one or more bacterial microbiologic studies. Pneumonia was primary viral in 174 of these patients and concomitant/secondary bacterial in 36.⁸ Similarly, in a study performed in United States,⁹ of 451 hospitalized patients on whom chest radiographs were performed, 195 (43%) had pneumonia (bacterial infections were reported in 13 patients with pneumonia). In other studies, the reported frequency of pneumonia in hospitalized patients ranged between 23% and 66%.¹⁰⁻¹² Pneumonia was associated with high morbidity, as assessed by the length of hospital stay and the rates of intensive care unit (ICU) admission and in-hospital complications, including mortality.^{8,9}

Pathological studies on autopsy samples from 100 patients with fatal influenza A(H1N1)pdm09 virus infection revealed that the virus targeted the lower respiratory tract, resulting in diffuse alveolar damage (edema, hyaline membranes, inflammation, and fibrosis), as manifested clinically by severe acute respiratory distress syndrome (ARDS) with refractory hypoxemia. However, a significant proportion of influenza A(H1N1)pdm09 case-patients in that report also showed

Table 1

Frequency of complications in hospitalized patients with influenza A(H1N1)pdm09 virus infection: data from the Spanish Network for the Research in Infectious Diseases cohort (585 patients)

Complications	no. (%)
Pneumonia	234/542 (43.1) ^a
Primary viral pneumonia	174/210 (82.8) ^b
Concomitant/secondary bacterial pneumonia	36/210 (17.1) ^b
ICU admission	71 (12.1)
Need for mechanical ventilation (endotracheal intubation)	36 (6.2)
Non-invasive mechanical ventilation	27 (4.6)
ARDS	23 (3.9)
Septic shock	21 (3.6)
Asthma exacerbation	45 (7.6)
COPD exacerbation	21 (3.6)
Nosocomial infections	16 (2.7)
Central venous catheter-related bacteremia	8 (1.4)
Ventilation-associated pneumonia	4 (0.7)
Nosocomial pneumonia not related with ventilation	5 (0.9)
Septic thrombophlebitis	2 (0.3)
Acute cardiac events	12 (2.1)
Heart failure	9 (1.5)
Arrhythmias	5 (0.9)
Acute coronary syndrome	1 (0.2)
Preterm delivery	2 (0.3)
Neurological complications	2 (0.3)
Acute kidney failure with renal replacement therapy	1 (0.2)
Diabetic ketoacidosis	1 (0.2)
In-hospital mortality	13 (2.2)

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit.

^aChest radiography was obtained on 542 patients.

^bOne or more bacterial microbiologic studies were performed on 210 patients with pneumonia.

viral localization along with inflammation or other histopathological changes in trachea, bronchi, or bronchioles.¹³ These pathological data have been found in other studies.¹⁴

Primary viral pneumonia

The first conclusive evidence that the influenza virus could cause pneumonia came during the 1958 to 1959 pandemic. Pathologic findings in pure influenza pneumonia include necrotizing bronchitis, hyaline membranes, intra-alveolar hemorrhage and edema, and interstitial inflammation.⁶

In the REIPI cohort of hospitalized patients with primary viral pneumonia, 124 (71.3%) were below the age of 50 and 98 (56.3%) were males. Nearly 50% of patients had underlying medical comorbidities, mainly chronic pulmonary disease (21.8%), immunosuppression (12.1%), diabetes mellitus (12.1%) and chronic cardiac disease (8.6%). Obesity (BMI > 30) was documented in 20.1% and pregnancy in seven women. The most frequent clinical features reported were fever, cough, arthromyalgia and dyspnea. Pleuritic chest pain was present in 21% of patients and gastrointestinal symptoms in 15%. Findings on physical examination included diffuse rales and wheezing. Radiographs revealed multilobar infiltrates in 63.2%. Forty-one (23.6%) required ICU admission and in-hospital mortality was 4.6%.⁸ It is significant that most patients requiring ICU

admission during the pandemic had respiratory failure due mainly to primary influenza pneumonia.¹⁵⁻¹⁷

In a Spanish study of patients requiring ICU admission, more than half (55.1%) of subjects with primary viral pneumonia were male and the mean age was 43 years. Mechanical ventilation was used in 70.2% of the patients, 60.2% with invasive modes and 23.1% with non-invasive. Obesity was the most frequent comorbidity (40.1%), followed by chronic obstructive pulmonary disease (COPD) (12.1%), diabetes (11%) and asthma (10.5%). Overall mortality was 17.7%.¹⁸

Secondary/concomitant bacterial pneumonia

It has long been recognized that influenza infection is closely associated with an increased incidence of bacterial pneumonia.¹⁹ In previous pandemics, secondary bacterial pneumonia was considered when a typical viral influenza infection was followed by near resolution, subsequently complicated 4 to 14 days later by a recurrence of fever, dyspnea, productive cough, and pulmonary consolidation. In contrast, concomitant bacterial pneumonia was considered when a bacterium was isolated during the first days of influenza virus infection onset.^{20,21} This classification had important implications for the etiologic agents identified in these patients.

During pandemic (H1N1) 2009, bacterial pneumonia was infrequent in Mexico and California.^{11,22} However, in studies of autopsy specimens, Shieh et al¹³ reported bacterial co-infection in 26 of 100 patients with fatal influenza A(H1N1)pdm09. Other studies found the frequency of bacterial pneumonia in patients requiring ICU admission to range between 20.3% and 32.1%.^{15,16} In the REIPI cohort, the prevalence of concomitant/secondary bacterial pneumonia was 17.2%. *Streptococcus pneumoniae* was the most frequent causative pathogen of bacterial co-infection in this cohort⁸ and in other studies.^{23,24} Several reports identified methicillin-resistant *Staphylococcus aureus* as the etiologic agent for secondary/concomitant bacterial pneumonia during the pandemic.²⁵ Other pathogens isolated were *Haemophilus influenzae*, *Streptococcus* spp., *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Aspergillus* sp.²⁶

Studies have reported an association between bacterial co-infection and disease severity.^{8,24} One study²⁷ found that 70% of patients with influenza A(H1N1)pdm09 virus infection and invasive group A *Streptococcus* died, compared with an overall mortality rate of 2-6% for hospitalized influenza A(H1N1)pdm09 patients in other studies.

Investigators have sought to determine the clinical features and factors associated with concomitant/secondary bacterial pneumonia. Compared with patients with primary viral pneumonia, patients with bacterial pneumonia in the REIPI cohort were more likely to have chronic liver disease, purulent sputum, tachycardia, pleural effusion, leukocytosis, and C-reactive protein (CRP) levels above 80 mg/L at hospital admission. Conversely, interstitial bilateral infiltrates in chest X-rays were more frequent in patients with primary viral pneumonia (Table 2).⁸ Moreover, Dhanoa et al.²⁸ reported that age >50 years, presence of comorbidity, liver impairment, development of complications, supplemental oxygen requirement, leukocytosis and neutrophilia were clinical factors associated with bacterial co-infection. Interestingly, studies have found that procalcitonin and CRP both alone and in combination can detect pneumonia of mixed bacterial infection in this context.^{29,30} Furthermore, patients with co-infection at ICU admission were older and presented a higher APACHE (Acute Physiology and Chronic Health Evaluation) II score and SOFA (Sequential Organ Failure Assessment) score compared with patients with primary viral pneumonia.³¹ Bacterial pneumonia presents distinctive radiographic features because it is often associated with pleural effusion, lymphadenopathy and lobar consolidations. Conversely, the characteristic imaging findings in primary viral pneumonia are ground-glass opacities with areas of consolidation.^{32,33}

Table 2

Characteristics of hospitalized patients with pandemic (H1N1) 2009 with primary viral pneumonia and bacterial coinfection from the Spanish Network for the Research in Infectious Diseases cohort

	Primary viral pneumonia (n=174)	Bacterial coinfection (n=36)	P value
Age, median (IQR), years	40 (50-51)	41.5 (29-47)	.90
Female sex	76 (43.7)	16 (44.4)	.93
Comorbidities	90 (51.7)	19 (52.8)	.90
Chronic heart disease	15 (8.6)	1 (2.8)	.31
Chronic pulmonary disease	38 (21.8)	8 (22.2)	.96
Chronic kidney disease	7 (4)	2 (5.6)	.65
Chronic liver disease	9 (5.2)	5 (13.9)	.05
Pneumococcal vaccine	7 (4.8)	0 (0)	.59
Current smoker	63 (36.3)	14 (40)	.67
Alcohol abuse	14 (8.1)	5 (14.3)	.33
Early oseltamivir treatment (< 72 hours)	57 (35)	11 (31.4)	.68
Clinical features			
Cough	156 (90.2)	34 (94.4)	.41
Shortness of breath	108 (62.1)	18 (50)	.17
Muscle aches	107 (61.5)	20 (55.6)	.50
Sore throat	46 (26)	7 (19.4)	.37
Headache	45 (25.9)	8 (22.2)	.64
Rhinorrhea	28 (16.1)	3 (8.3)	.23
Diarrhea	25 (14.3)	4 (11.1)	.79
Vomiting	27 (15.5)	8 (22.2)	.32
Pleuritic chest pain	38 (21.8)	13 (36.1)	.06
Physical findings			
Hypotension (SBP ≤90 mmHg)	10 (6.1)	2 (6.1)	.99
Tachypnea (24 breaths/min)	67 (57.3)	14 (70)	.28
Tachycardia (90 bpm)	91 (58.7)	27 (84.4)	.006
Impaired consciousness	7 (4)	3 (8.3)	.38
Purulent sputum	41 (24.7)	16 (47.1)	.001
Specific-CAP scores			
High-risk PSI classes (IV-V) ^a	21 (12.2)	6 (18.2)	.46
High-risk CURB-65 groups (2-3) ^b	25 (14.5)	5 (15.6)	.88
Laboratory and radiographic findings			
Leukocytosis (>12,000 mm ³)	24 (13.8)	9 (25)	.09
Hyponatremia (<135 mEq/L)	56 (32.6)	15 (41.7)	.29
Hypoxemia (O ₂ saturation <90%)	40 (28.8)	8 (28.6)	.98
C-reactive protein (>80 U/mL)	68 (39.4)	23 (63.6)	.03
Interstitial infiltrates	53 (30.5)	5 (13.9)	.05
Lobar infiltrates	46 (26.4)	14 (38.9)	.33
Pleural effusion	9 (5.2)	8 (22.2)	.002

IQR: interquartile range; PSI: pneumonia severity index; SBP: systolic blood pressure.

^aPatients were stratified into the following risk classes according to the PSI score: low risk (≤90 points, classes I, II, and III) and high risk (>90 points, classes IV and V).

^bPatients were stratified into the following risk groups according to the CURB-65 score: low risk (≤1 points, groups 0 and 1) and high risk (≥2 points, groups 2 and 3).

Exacerbations of chronic pulmonary diseases

Infectious agents are recognized as a major pathogenic factor in exacerbations of chronic pulmonary diseases. The relevance of viral infections has been studied in exacerbations of COPD and asthma.

Rhinovirus, coronavirus, respiratory syncytial virus, and influenza are the main viral pathogens that cause exacerbations.^{6,34,35}

Chronic pulmonary diseases, mainly COPD and asthma, are frequent comorbidities reported in hospitalized patients with influenza A(H1N1)pdm09 virus infection.^{8,9,11} Information about clinical features and prognosis from these groups of patients during pandemic is scarce; most of the information available comes from hospitalized asthmatic children.³⁶

In the REIPI cohort, 49 (8.4%) patients had COPD and 104 (17.8%) had asthma. Pneumonia was documented in 17 COPD patients. Of the 32 COPD patients without pneumonia, 21 (65.6%) had exacerbation of pulmonary disease (evidence of wheezing at hospital admission). Among patients with COPD exacerbation, five required ICU admission (three needed mechanical ventilation); there were no deaths. Bacterial co-infection was documented in only one COPD patient. Moreover, pneumonia was documented in 24 asthma patients (chest X-rays were performed in 100 asthma patients). Of the 76 asthma patients without pneumonia, 45 (59.2%) had exacerbations of pulmonary disease. Among patients with asthma exacerbation, seven required ICU admission (two needed mechanical ventilation) and none died. Bacterial co-infection was not documented in these patients.

Severe disease (intensive care unit admission and mortality)

Characteristics of ICU patients and clinical outcomes of the REIPI cohort were similar to those described elsewhere.^{15-17,37} Although our mortality rate was lower than that reported in the earliest studies of hospitalized patients, it was similar to that of other studies.^{38,39}

Severe disease occurred in 75 patients (12.8%), of whom 71 required ICU admission and 13 died. Among the 71 patients requiring ICU admission, 53 had pneumonia, 52 underwent mechanical ventilation, and 23 developed ARDS. Fifty-two (73.2%) of the 71 ICU patients had chronic comorbid conditions, mainly chronic pulmonary disease (33 patients), chronic heart disease (10), diabetes mellitus (10) and immunosuppression (7). Only 2 of 98 pregnant women required ICU admission.⁴⁰

In-hospital mortality was 2.2% (13 of 585 patients). The median time from hospital admission to death was nine days (range 1-33). Among the 13 patients who died, nine were under 50 years of age, eight were women, 12 had comorbid conditions, two had morbid obesity, 11 had multilobar pneumonia, and five had bacterial co-infection. Causes of death were respiratory failure/acute respiratory distress syndrome (3 out of 13 patients), shock/multiorgan failure (4 patients), decompensated comorbid conditions (4) and nosocomial infection (2).⁴⁰

In the REIPI cohort, independent factors associated with severe disease were younger age, chronic comorbid conditions, morbid obesity and bacterial co-infection. Conversely, early oseltamivir therapy was a protective factor.⁴⁰ In another study,¹⁵ investigators identified all patients with confirmed influenza A(H1N1)pdm09 virus infection who were admitted to Australian or New Zealand ICUs during winter 2009. Interestingly, the number of ICU admissions due to influenza A(H1N1)pdm09 was 15 times higher than that due to viral pneumonitis in previous years. Infants and younger adults were found to be at particular risk of ICU admission. Pregnant women, obesity, and indigenous Australian and New Zealand populations also appeared to have an increased risk. In-hospital mortality exceeded 16%. Furthermore, in ICU patients in Canada,¹⁶ influenza A(H1N1)pdm09 affected primarily young, female, and aboriginal patients without major comorbidities; 28-day mortality was 14.3%. Chronic lung disease, obesity, hypertension, and diabetes were the most common comorbidities. Critical illness occurred rapidly after hospital admission and was associated with severe oxygenation failure, a need for prolonged mechanical ventilation, and the frequent use of rescue therapies such as extracorporeal

Table 3

Factors associated with intensive care unit admission or mortality in patients with influenza A(H1N1)pdm09 virus infection^{15,16,40-46}

Younger age	Glucocorticoid use
Comorbidities	Delayed antiviral therapy
Obesity	Immunosuppression
Bacterial co-infection	Dyspnea at admission
Indigenous populations	Altered mental status at admission
Pregnancy	Hypoxemia
Pneumonia	Elevated CRP, LDH, CK or transaminases at admission

CRP: C-reactive protein; CK: creatine kinase; LDH: lactate dehydrogenase.

membrane oxygenation. Factors associated with ICU admission or mortality during pandemic (H1N1) 2009 are detailed in Table 3. It is important to note that we documented that influenza A(H1N1)pdm09 was not associated with poorer outcomes in hospitalized pregnant women compared with non-pregnant women of reproductive age in a context of early diagnosis and antiviral therapy.⁴¹ Similarly, in the REIPI cohort, well controlled on HAART HIV patients had a similar clinical outcomes and prognosis to that of non-HIV patients.⁴²

Interestingly, CAP-specific scores demonstrated moderate usefulness for predicting ICU admission and/or mortality in hospitalized patients with influenza A(H1N1)pdm09 complicated by pneumonia in the REIPI cohort and other studies.^{8,47} Consistent with these data, severity assessment tools (general severity of illness and CAP-specific scores) undervalued prognosis and should not be used as instruments to guide decisions on patients requiring ICU admission.⁴⁸ A limitation of these scores is that age is the variable with the most weight, and most patients affected by pneumonia during pandemic were younger adults. In addition, other risk factors for severe influenza A(H1N1)pdm09 such as obesity were not included in these scores.

Miscellaneous complications

In addition to respiratory complications of viral influenza, several other complications due to direct and indirect effects on other body systems have been reported to be associated with influenza A(H1N1)pdm09 virus infection.

Influenza virus frequently exacerbates underlying heart problems and has been associated with triggering myocardial infarction.⁴⁹ In the REIPI cohort, 12 patients had concurrent acute cardiac events during hospitalization (nine had acute heart failure, five had arrhythmias and one had acute coronary syndrome). Among these patients, seven were over 50 years old, ten had comorbid conditions (mainly chronic heart disease and COPD) and five were current smokers. Regarding outcomes, two had pneumonia, ten required ICU admission, and one died. Interestingly, other studies documented myocarditis, pericarditis, electrocardiographic abnormalities and left ventricular systolic dysfunction concurrent with influenza A(H1N1)pdm09 virus infection.⁵⁰⁻⁵²

It is well known that influenza has neurological manifestations and complications. Neurological complications of influenza include encephalopathy, encephalomyelitis, transverse myelitis, aseptic meningitis, focal neurological disorders, and Guillain-Barre Syndrome. Most cases occur in children.⁶ In a recent study on hospitalized pediatric patients with influenza A(H1N1)pdm09 infection,⁵³ the most common manifestation was seizure with underlying neurological disease followed by encephalopathy with or without neuroimaging changes. In another study, the primary influenza-associated neurologic complications were encephalopathy/encephalitis, seizures, meningitis, and Guillain-Barre Syndrome.⁵⁴ In

the REIPI cohort of adult patients, two developed neurological complications: one had meningoencephalitis and the other acute visual disturbances related to oseltamivir treatment.

Nosocomial infections were reported in 16 patients in the REIPI cohort, mainly catheter-associated bacteremia and nosocomial pneumonia. In this regard, influenza viruses have been reported to cause immune defects.⁵⁵ In addition, our data⁵⁶ and those of other studies⁵⁷ suggest that patients with influenza infection receiving corticosteroids present higher rates of nosocomial infections and sepsis.

Other complications reported during influenza were myositis and rhabdomyolysis, Reye's syndrome, and preterm delivery. Psychiatric complications after influenza infection are considered controversial.⁶ Acute kidney failure was also reported, with some patients requiring renal replacement therapy. Risk factors for acute kidney injury included age, obesity, chronic kidney disease, and elevated creatine kinase.⁵⁸

Conclusions

Complications of influenza A(H1N1)pdm09 virus were frequent and involved numerous organ systems. The main complications were pneumonia, ICU admission (ARDS, septic shock, mechanical ventilation), exacerbations of chronic pulmonary diseases, nosocomial infections, and acute cardiac events. Most hospitalized patients with pneumonia had primary viral pneumonia; mortality, though low, occurred mainly in patients with this complication. Younger age, comorbidities, morbid obesity and bacterial co-infection were risk factors for severe disease. Influenza A(H1N1)pdm09-related complications were associated with increased morbidity and mortality.

Funding

This study was supported by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, (Ministry of Science and Innovation, Carlos III Health Institute), Programa de Investigación sobre gripe A/H1N1 (Influenza A/H1N1 Research Program) (Grant: GR09/0014), and co-financed by European Regional Development Fund "A way to achieve Europe", Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008). Dr. Viasus is the recipient of a research grant from the Institut d'Investigació Biomèdica de Bellvitge (Biomedical Research Institute of Bellvitge, IDIBELL).

Conflicts of interest

All authors declare that they have no conflicts of interest in this article.

References

- Pérez-Padilla R, De la Rosa-Zamboni D, Ponce de León S, Hernández M, Quiñones-Falconi F, Bautista E, et al; INER Working Group on Influenza. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med.* 2009;361:680-9.
- Surveillance Group for New Influenza A(H1N1) Virus Investigation and Control in Spain. New influenza A(H1N1) virus infections in Spain, April-May 2009. *Euro Surveill.* 2009;14:19209.
- Viasus D, Cordero E, Rodríguez-Baño J, Oteo JA, Fernández-Navarro A, Ortega L, et al; Novel Influenza A (H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI). Changes in epidemiology, clinical features and severity of influenza A (H1N1) 2009 pneumonia in the first post-pandemic influenza season. *Clin Microbiol Infect.* 2012;18:E55-62.
- Athanasios M, Baka A, Andreopoulou A, Spala G, Karageorgou K, Kostopoulos L, et al. Influenza surveillance during the post-pandemic influenza 2010/11 season in Greece, 04 October 2010 to 22 May 2011. *Euro Surveill.* 2011;16:20004.
- Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyekii TM, Zaki SR. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med.* 2010;362:1708-19.
- Rothberg MB, Haessler SD, Brown RB. Complications of viral influenza. *Am J Med.* 2008;121:258-64.
- Itoh Y, Shinya K, Kiso M, Watanabe T, Sakoda Y, Hatta M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. *Nature.* 2009;460:1021-5.
- Viasus D, Paño-Pardo JR, Pachón J, Riera M, López-Medrano F, Payeras A, et al. Novel Influenza A(H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI). Pneumonia complicating pandemic (H1N1) 2009: risk factors, clinical features, and outcomes. *Medicine (Baltimore).* 2011;90:328-36.
- Jain S, Benoit SR, Skarbinski J, Bramley AM, Finelli L; for the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Influenza-Associated Pneumonia Among Hospitalized Patients With 2009 Pandemic Influenza A (H1N1) Virus—United States, 2009. *Clin Infect Dis.* 2012;54:1221-9.
- Cullen G, Martin J, O'Donnell J, Boland M, Canny M, Keane E, et al. Surveillance of the first 205 confirmed hospitalised cases of pandemic H1N1 influenza in Ireland, 28 April - 3 October 2009. *Euro Surveill.* 2009;14:19389.
- Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med.* 2009;361:1935-44.
- Louie JK, Acosta M, Winter K, Jean C, Gavalí S, Schechter R, et al. California Pandemic (H1N1) Working Group. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA.* 2009;302:1896-902.
- Shieh WJ, Blau DM, Denison AM, Deleon-Carnes M, Adem P, Bhatnagar J, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. *Am J Pathol.* 2010;177:166-75.
- Nin N, Sánchez-Rodríguez C, Ver LS, Cardinal P, Ferruelo A, Soto L, et al. Lung histopathological findings in fatal pandemic influenza A (H1N1). *Med Intensiva.* 2012;36:24-31.
- ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med.* 2009;361:1925-34.
- Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Canadian Critical Care Trials Group H1N1 Collaborative. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA.* 2009;302:1872-9.
- Rello J, Rodríguez A, Ibáñez P, Socías L, Cebrán J, Marques A, Guerrero J, et al. H1N1 SEMICYUC Working Group. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care.* 2009;13:R148.
- Díaz E, Martín-Loeches I, Canadell L, Vidaur L, Suárez D, Socías L, et al. H1N1 SEMICYUC-CIBERES-REIPI Working Group (GETGAG). Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. *J Infect.* 2012;64:311-8.
- Klugman KP, Chien YW, Madhi SA. Pneumococcal pneumonia and influenza: a deadly combination. *Vaccine.* 2009;27:C9-14.
- Louria DB, Blumenfeld HL, Ellis JT, Kilbourne ED, Rogers DE. Studies on influenza in the pandemic of 1957-1958. II. Pulmonary complications of influenza. *J Clin Invest.* 1959;38:213-65.
- Oswald NC, Shooter RA, Curwen MP. Pneumonia complicating Asian influenza. *Br Med J.* 1958;2:1305-11.
- Echevarría-Zuno S, Mejía-Arangur JM, Mar-Obeso AJ, Grajales-Muñiz C, Robles-Pérez E, González-León M, et al. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. *Lancet.* 2009;374:2072-9.
- Estenssoro E, Ríos FG, Apezteguía C, Reina R, Neira J, Ceraso DH, et al. Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med.* 2010;182:41-8.
- Palacios G, Hornig M, Cisterna D, Savji N, Bussetti AV, Kapoor V, et al. *Streptococcus pneumoniae* coinfection is correlated with the severity of H1N1 pandemic influenza. *PLoS One.* 2009;4:e8540.
- Murray RJ, Robinson JO, White JN, Hughes F, Coombs GW, Pearson JC, et al. Community-acquired pneumonia due to pandemic A(H1N1)2009 influenza virus and methicillin resistant *Staphylococcus aureus* co-infection. *PLoS One.* 2010;5:e8705.
- García-Vidal C, Barba P, Arnan M, Moreno A, Ruiz-Camps I, Gudiol C, et al. Invasive aspergillosis complicating pandemic influenza A (H1N1) infection in severely immunocompromised patients. *Clin Infect Dis.* 2011;53:e16-9.
- Jean C, Louie JK, Glaser CA, Harriman K, Hacker JK, Aranki F, et al. Invasive group A streptococcal infection concurrent with 2009 H1N1 influenza. *Clin Infect Dis.* 2010;50:e59-62.
- Dhanoo A, Fang NC, Hassan SS, Kaniappan P, Rajasekaram G. Epidemiology and clinical characteristics of hospitalized patients with pandemic influenza A (H1N1) 2009 infections: the effects of bacterial coinfection. *Virol J.* 2011;8:501.
- Guerilly C, Coisel Y, Botelho-Nevers E, Dizier S, Castanier M, Lepaul-Ercole R, et al. Significance of high levels of procalcitonin in patients with influenza A (H1N1) pneumonia. *J Infect.* 2010;61:355-8.
- Ahn S, Kim WY, Kim SH, Hong S, Lim CM, Koh Y, et al. Role of procalcitonin and C-reactive protein in differentiation of mixed bacterial infection from 2009 H1N1 viral pneumonia. *Influenza Other Respi Viruses.* 2011;5:398-403.
- Martín-Loeches I, Sánchez-Corral A, Díaz E, Granada RM, Zaragoza R, Villavicencio C, et al. H1N1 SEMICYUC Working Group. Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A(H1N1) virus. *Chest.* 2011;139:555-62.
- Abbo L, Quartin A, Morris MI, Saigal G, Ariza-Heredia E, Mariani P, et al. Pulmonary imaging of pandemic influenza H1N1 infection: relationship between clinical presentation and disease burden on chest radiography and CT. *Br J Radiol.* 2010;83:645-51.

33. Cunha B, Syed U, Strollo S. During the "herald wave" of the pandemic bacterial pneumonia relatively rare with fatal swine influenza (H1N1) pneumonia: if chest films have no focal segmental/lobar infiltrates, antibiotic therapy is unnecessary. *J Chemother.* 2009;21:584-9.
34. Ko FW, Ip M, Chan PK, Fok JP, Chan MC, Ngai JC, et al. A 1-year prospective study of the infectious etiology in patients hospitalized with acute exacerbations of COPD. *Chest.* 2007;131:44-52.
35. Rohde G, Wiethage A, Borg I, Kauth M, Bauer TT, Gillissen A, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax.* 2003;58:37-42.
36. Dawood FS, Kamimoto L, D'Mello TA, Reingold A, Gershman K, Meek J, et al. Children with asthma hospitalized with seasonal or pandemic influenza, 2003-2009. *Pediatrics.* 2011;128:e27-32.
37. Miller RR 3rd, Markewitz BA, Rolfs RT, Brown SM, Dascomb KK, Grissom CK, et al. Clinical findings and demographic factors associated with intensive care unit admission in Utah due to 2009 novel influenza A (H1N1) infection. *Chest.* 2010;137:752-8.
38. Verrall A, Norton K, Rooker S, Dee S, Olsen L, Tan CE, et al. Hospitalizations for pandemic (H1N1) 2009 among Maori and Pacific Islanders, New Zealand. *Emerg Infect Dis.* 2010;16:100-2.
39. Cullen G, Martin J, O'Donnell J, Boland M, Canny M, Keane E, et al. Surveillance of the first 205 confirmed hospitalised cases of pandemic H1N1 influenza in Ireland, 28 April - 3 October 2009. *Euro Surveill.* 2009;14:19389.
40. Viasus D, Paño-Pardo JR, Pachón J, Campins A, López-Medrano F, Villoslada A, et al. Factors associated with severe disease in hospitalized adults with pandemic (H1N1) 2009 in Spain. *Clin Microbiol Infect.* 2011;17:738-46.
41. Paño-Pardo JR, Rodríguez-Baño J, Martínez-Sánchez N, Viasus D, Fariñas MC, Leyes M, et al. Prognosis of 2009 A(H1N1) influenza in hospitalized pregnant women in a context of early diagnosis and antiviral therapy. *Antivir Ther.* 2011. doi: 10.3851/IMP2019.
42. Riera M, Payeras A, Marcos MA, Viasus D, Fariñas MC, Segura F, et al. Clinical presentation and prognosis of the 2009 H1N1 influenza A infection in HIV-1-infected patients: a Spanish multicenter study. *AIDS.* 2010;24:2461-7.
43. Han K, Ma H, An X, Su Y, Chen J, Lian Z, et al. Early use of glucocorticoids was a risk factor for critical disease and death from pH1N1 infection. *Clin Infect Dis.* 2011;53:326-33.
44. Van Kerkhove MD, Vandemaële KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Med.* 2011;8:e1001053.
45. Gilca R, De Serres G, Boulianne N, Ouhoumane N, Papenburg J, Douville-Fradet M, et al. Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. *Influenza Other Respi Viruses.* 2011;5:247-55.
46. Viasus D, Paño-Pardo JR, Pachón J, Riera M, López-Medrano F, Payeras A, et al. Timing of oseltamivir administration and outcomes in hospitalized adults with pandemic 2009 influenza A(H1N1) virus infection. *Chest.* 2011;140:1025-32.
47. Brandão-Neto RA, Goulart AC, Santana AN, Martins HS, Ribeiro SC, Ho LY, et al. The role of pneumonia scores in the emergency room in patients infected by 2009 H1N1 infection. *Eur J Emerg Med.* 2012;19:200-2.
48. Pereira JM, Moreno RP, Matos R, Rhodes A, Martin-Loeches I, Cecconi M, et al. Severity assessment tools in ICU patients with 2009 Influenza A (H1N1) pneumonia. *Clin Microbiol Infect.* 2012;18:1040-8.
49. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis.* 2009;9:601-10.
50. Erden I, Erden EC, Ozhan H, Basar C. Acute myocarditis mimicking acute myocardial infarction associated with pandemic 2009 (H1N1) influenza A virus. *Cardiol J.* 2011;18:552-5.
51. Chacko B, Peter JV, Pichamuthu K, Ramakrishna K, Moorthy M, Karthik R, et al. Cardiac manifestations in patients with pandemic (H1N1) 2009 virus infection needing intensive care. *J Crit Care.* 2012;27:106.e1-6.
52. Akritidis N, Mastora M, Baxevanos G, Dimos G, Pappas G. Electrocardiographic abnormalities in patients with novel H1N1 influenza virus infection. *Am J Cardiol.* 2010;106:1517-9.
53. Kedia S, Stroud B, Parsons J, Schreiner T, Curtis DJ, Bagdure D, et al. Pediatric neurological complications of 2009 pandemic influenza A (H1N1). *Arch Neurol.* 2011;68:455-62.
54. Glaser C, Winter K, Dubray K, Harriman K, Uyeki TM, Sejvar J, et al. A Population-Based Study of Neurologic Manifestations of Severe Influenza A(H1N1)pdm09 in California. *Clin Infect Dis.* 2012;55:514-20.
55. Lewis DE, Gilbert BE, Knight V. Influenza virus infection induces functional alterations in peripheral blood lymphocytes. *J Immunol.* 1986;137:3777-81.
56. Viasus D, Paño-Pardo JR, Cordero E, Campins A, López-Medrano F, Villoslada A, et al. Effect of immunomodulatory therapies in patients with pandemic influenza A (H1N1) 2009 complicated by pneumonia. *J Infect.* 2011;62:193-9.
57. Fujii T, Nakamura T, Iwamoto A. Current concepts in SARS treatment. *J Infect Chemother.* 2004;10:1-7.
58. Demirjian SG, Raina R, Bhimraj A, Navaneethan SD, Gordon SM, Schreiber MJ Jr, et al. 2009 influenza A infection and acute kidney injury: incidence, risk factors, and complications. *Am J Nephrol.* 2011;34:1-8.