Pandemic 2009 Influenza A in Argentina

A Study of 337 Patients on Mechanical Ventilation

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***Rationale*: The rapid spread of the 2009 Influenza A (H1N1) around the world underscores the need for a better knowledge of epidemiology, clinical features, outcomes, and mortality predictors, especially in the most severe presentations.**

***Objectives*: To describe these characteristics in patients with confirmed, probable, and suspected viral pneumonia caused by 2009 influenza A (H1N1) admitted to 35 intensive care units with acute respiratory failure requiring mechanical ventilation in Argentina, between June 3 and September 7.**

***Methods*: Inception-cohort study including 337 consecutive adult patients. Data were collected in a form posted on the Argentinian Society of Intensive Care website.**

***Measurements and Main Results*: Proportions of confirmed, probable, or suspected cases were 39%, 8%, and 53% and had similar outcomes. APACHE II was 18 ± 7; age 47 ± 17 years; 56% were male; and 64% had underlying conditions, with obesity (24%), chronic obstructive respiratory disease (18%), and immunosupression (15%) being the most common. Seven percent were pregnant. On admission, patients had severe hypoxemia (Pa_{O_2}/FI_{O_2} 140 [87–200]), extensive lung radiologic infiltrates (2.87 ± 1.03 quadrants) and bacterial coinfection, (25%; mostly with *Streptococcus pneumoniae*). Use of adjuvants such as recruitment maneuvers (40%) and prone positioning (13%), and shock (72%) and acute kidney injury requiring hemodialysis (17%), were frequent. Mortality was 46%, and was similar across all ages. APACHE II, lowest Pa_{O_2}/FI_{O_2}, shock, hemodialysis, prone positioning, and *S. pneumoniae* coinfection independently predicted death.**

***Conclusions*: Patients with 2009 influenza A (H1N1) requiring mechanical ventilation were mostly middle-aged adults, often with comorbidities, and frequently developed severe acute respiratory distress syndrome and multiorgan failure requiring advanced organ support. Case fatality rate was accordingly high.**

Keywords: ARDS; virus; mechanical ventilation; refractory hypoxemia; multiple organ dysfunction

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Pandemic influenza A (H1N1) emerged in April of 2009 and rapidly spread throughout the world. Though the majority of the patients undergo a benign course of disease, some present with acute respiratory failure requiring intensive care unit (ICU) admission for mechanical ventilation, with a subsequent high mortality.

What This Study Adds to the Field

This study, one of the largest cohorts of the sickest patients with 2009 Influenza A (H1N1), characterized these patients as middle-aged, and predominantly male, with frequent comorbidities and severe acute respiratory distress syndrome. Most patients died primarily of refractory hypoxemia; but nonpulmonary organ failure, shock and acute kidney failure, sometimes requiring hemodyalisis, was also very common. Late ICU admission and coexistent infection with *Streptococcus pneumoniae* on admission worsened patient outcome.

New diseases, or diseases that acquire distinctive characteristics on their presentation and evolution, pose a challenge to the clinician. When an emergent infectious disease becomes pandemic and causes severe illness and significant mortality rates, the situation evolves into a major public health problem. By January 2, 2010, more than 208 countries worldwide had reported laboratory-confirmed cases of pandemic 2009 influenza A (H1N1), including at least 12,220 deaths (1). The seasonal behavior of influenza offers the opportunity to assess the outbreaks occurring during winters in the Southern and Northern hemispheres sequentially. In Argentina, the first case occurred on April 25, 2009; the virus started to circulate rapidly after May 17 and peaked between June 20 and July 3, with dissemination over the entire country (2). As of January 2, 2010, there had been 1,390,566 cases of influenza-like illness (ILI) (3); 14,034 were admitted to the hospital, with 617 deaths ensuing among them (4.4%) (2).

A massive admission of patients with severe pneumonia, many of them young and in previous good health, crowded the hospitals—within a scenario involving a lack of epidemiologic and clinical data—and generated uncertainty and stress in the intensive care unit (ICU) staff, until the early reports from Mexico were published showing some of the distinctive features

of the illness (4–6). As did other intensive-care societies, the Society of Intensive Care of Argentina (SATI) foresaw the risks and challenges of the situation (7) and on June 27, 2009 uploaded to the society website a voluntary Registry of Cases to answer the following questions:

1. What was the frequency of adult patients admitted to ICUs during the 2009 Influenza A (H1N1) pandemic with acute respiratory failure with ILI and viral pneumonia necessitating mechanical ventilation (MV)?
2. What were the main risk factors, the clinical and physiological characteristics, and the complications?
3. What was the hospital mortality, and what were the conditions independently associated with that outcome?

METHODS

Design of the Study and of the Registry

This was an inception-cohort study that included patients aged 15 years or more admitted to the ICU with ILI and acute respiratory failure requiring MV, during the winter season in the Southern Hemisphere. Data were collected online in a form designed by experts of the SATI that, after pilot testing, was finally posted at the Society website on June 27. Also included was an instruction form containing operational definitions. Information was recorded both prospectively and retrospectively. All this information was also available, on request, in paper form. Each participating center filled out a form describing the characteristics of the hospital and of its ICU. Records were controlled for errors, and local researchers were contacted by the study authors (E.E. and F.G.R.), if needed.

Data Collection

On ICU admission, respiratory specimens were collected from each patient and tested for the 2009 influenza A (H1N1) virus. Most samples nationwide were submitted initially to a central reference laboratory to perform a real-time polymerase-chain-reaction (RT-PCR) analysis. Many could not be analyzed, however, because diagnostic laboratories soon became overwhelmed. As of September 25, 2009, the national health authorities had made the announcement that the novel 2009 influenza A (H1N1) virus had displaced other respiratory viruses in patients 5 years or older and, together with other unidentified influenza A viruses, constituted 93.4% of the samples processed (2). A seasonal influenza A virus was found in fewer than 2% of the samples. In view of this information, included in the study were both probable and suspected cases (8) that fulfilled the criteria of ILI and acute respiratory failure necessitating MV. Samples were also analyzed for the diagnosis of concomitant bacterial pneumonia.

The following data were also recorded: severity of illness by the APACHE II score, age, sex, underlying diseases (defined as: immunosuppression, chronic obstructive pulmonary disease [COPD], asthma, diabetes, chronic heart failure, chronic renal failure, cirrhosis), vaccination for seasonal influenza A within the current year, pregnancy or childbirth, habitual smoking, height and estimated or measured body weight for body mass index (BMI) calculation, or the absence of any risk factor. Obesity was defined as a BMI greater than 30. We recorded the time in days from symptom onset to hospital admission and from hospital admission to MV initiation; the place in which MV was started (e. g., the ICU, the emergency department [ED], or the coronary care unit [CCU]); and, finally, the time from hospital admission to ICU admission. The extension of lung infiltrates on chest X-ray was registered as the number of quadrants involved and the Lung Injury Score calculated (9).

On a daily basis, we collected the results of arterial blood gases, oxygenation variables, progression to acute respiratory distress syndrome (ARDS) (10), and data of MV, which included the use of noninvasive ventilation (NIV), the concurrent use of MV adjuvants (recruitment maneuvers, prone positioning, or tracheal gas insufflation [TGI]), the occurrence of ventilator-associated pneumonia (VAP), and the need for inotropic drugs. The use and dosage of oseltamivir—the only neuraminidase inhibitor available in Argentina—along with the treatment of possible concurrent bacterial pneumonia were recorded as well. Newly developed acute kidney injury requiring hemodialysis and measurement of creatine-kinase levels (IU/L) were also registered.

The main measurement with respect to outcome was hospital mortality. The lengths of MV, of ICU, and of hospital stay were calculated.

Data Analysis

The descriptive statistics used were the means ± SD, or the medians and interquartile ranges (IQR) for continuous variables of normal and non-normal distributions, and frequency analysis (as percentages) for categorical data. The main comparisons performed were between survivors and nonsurvivors by means of unpaired *t* test, Wilcoxon rank-sum test, and either Fisher's exact test or Chi-square test, as appropriate. A P value of less than 0.05 was considered significant. The proportions of confirmed, probable, and suspected cases between survivors and nonsurvivors were also explored. The incidence of bacterial pneumonia, and especially that of *Streptococcus pneumoniae*, was analyzed in confirmed versus nonconfirmed (probable + suspected) cases.

A bivariate analysis for hospital mortality was performed and variables showing a P value of less than 0.20 included in a multivariable logistic-regression analysis in search of independent predictors of hospital mortality. A predictive model was built, and the goodness-of-fit assessed with the Hosmer-Lemeshow test. Discrimination of the model was evaluated by the area under a receiver-operating characteristic (ROC) curve. A Kaplan-Meier curve was constructed to evaluate survival over the follow-up period.

All analyses were performed with STATA 9 software. (Stata Corporation, College Station, TX)

Since no intervention was performed, informed consent was waived by institutional review boards.

RESULTS

Characteristics of the Hospitals

A brief description of the SATI and of some characteristics of the participating centers is displayed in the online supplement (*see* Tables E1 and E2). Thirty-five medical-surgical ICUs participated in the study; all constituting centers of high-acuity care for critically ill patients. Fourteen ICUs (40%) belonged to university or university-affiliated hospitals. The mean numbers of hospital and ICU beds were 216 ± 143 and 13 ± 10, respectively. The annual admissions to the ICUs were 709 ± 539, while 45% ± 20 of the patients usually require MV.

Clinical Characteristics of the Patients

Between June 6 and August 28, 2009, 337 adult patients with confirmed, probable, or suspected cases of 2009 influenza A (H1N1) with acute respiratory failure requiring MV were admitted to 35 ICUs. Most initiated MV in the ICU itself. The collection of all data performed in 214 patients was prospective (60%, admitted after June 29), while in the remaining patients the registry was partially prospective. Hospital and ICU admissions were more frequent between June 21 and July 12, peaking on June 28 and then gradually decreasing (Figure E1).

Since no differences in mortality were found among confirmed, probable, and suspected cases (Table 1), the population was analyzed as a single group.

In all but two patients, respiratory samples were obtained with nasopharyngeal swabs or tracheal aspirates for detection of viruses and other microorganisms. Treatment with oseltamivir was given to 98% of patients, with 60% receiving 300 mg/day. The frequency of use and doses were similar in both survivors

TABLE 1. EPIDEMIOLOGY, RISK FACTORS, AND OSELTAMIVIR USE IN THE ENTIRE POPULATION, AND COMPARISONS BETWEEN SURVIVORS AND NONSURVIVORS.

	All (*n = 337*)	Survivors (*n = 181*)	Nonsurvivors (*n = 156*)	*P* Value
Age, yr	47 ± 17	47 ± 17	46 ± 17	0.56
Sex, F/M	149/188 (44/56)	90/91 (50/50)	59/97 (38/62)	0.03
APACHE II score	18 ± 7	16 ± 6	20 ± 8	<0.001
Confirmed/probable/suspected cases	132/27/177 (39)/(8)/(53)	68/16/97 (38)/(9)/(53)	64/11/80 (42)/(7)/(51)	0.67 prob. vs. conf 0.52 susp. vs. conf.
Previous seasonal influenza vaccination	14/334 (4)	7/180 (4)	7/157 (5)	0.77
Habitual smoking	49/191 (26)	26/102 (26)	23/89 (26)	0.96
COPD	61/337 (18)	33/181 (18)	28/156 (18)	0.81
Asthma	18/337 (5)	9/181 (5)	9/156 (6)	0.75
Immunosuppression*	50/332 (15)	21/176 (12)	29/156 (19)	0.09
Obesity (BMI >30)	80/337 (24)	39/181 (22)	41/156 (26)	0.31
Diabetes	41/337 (12)	23/181 (13)	18/156 (12)	0.74
Chronic heart failure	35/337 (10)	17/181 (9)	18/156 (12)	0.52
Chronic renal failure in hemodialysis	15/337 (4)	7/181 (4)	8/156 (5)	0.58
Cirrhosis	9/337 (3)	3/181 (2)	6/156 (4)	0.21
Pregnancy	22/337 (7)	12/181 (7)	10/156 (6)	0.93
No known risk factor	121/336 (36)	71/181 (39)	51/156 (33)	0.24
Concomitant pneumonia with *S. pneumoniae* on admission	28 (8.3)	11 (6.1)	17 (10.9)	0.11
Oseltamivir use	328/336 (98)	178/181(98)	150/155 (97)	0.35
Oseltamivir dose (300/150/<150 mg/day)	194/113/17 (60)/(35)/(5)	106/58/12 (60)/(33)/(7)	88/55/5 (60)/(37)/(3)	0.58 150 vs. 300 0.21 <150 vs. 300

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index, calculated as weight in kilograms divided by height in squared meters conf. = confirmed;; COPD = chronic obstructive pulmonary disease; prob. = probable; susp. = suspected.

Data are expressed as number, (%), or mean ± SD.

* Includes oncohematologic disease (leukemia, lymphoma, and others); bone marrow transplantation; solid organ transplantation; human immunodeficiency virus infection; treatment with immunosuppressants, radiation or chemotherapy; recent treatment with high dose corticosteroids, or prolonged treatment with a daily dose of, or equivalent to, 1 mg/kg or 40 mg/day of prednisone.

and nonsurvivors. In all cases, antibiotic treatment for possible associated bacterial and atypical pneumonia was started. Prior seasonal influenza vaccination was infrequent.

The epidemiologic characteristics, severity of illness, and usual risk factors for 2009 influenza A (H1N1) for the whole population, as well as the comparisons between survivors and nonsurvivors, are displayed in Table 1. Of note, patients were middle-aged and predominantly male, especially in the nonsurvivor group. The most frequent previous conditions found in 64% of the patients were habitual smoking, obesity, COPD, and immunosuppression.

Pregnancy was common (n = 22; 7%), with 17 of the pregnant women being in the third trimester, 4 in the second, and 1 in the first (ending in a spontaneous abortion). The most frequent comorbidities were asthma (n = 3) and diabetes (n = 1), and none of these patients had received a prior seasonal influenza vaccination.

There were no differences in the distribution between survivors and nonsurvivors with respect to underlying conditions. A risk factor could not be identified in 36% of the patients. These latter were younger (41 ± 16 vs. 50 ± 17 yr, $P < 0.001$) and had lower APACHE II scores (16 ± 7 vs. 19 ± 8, $P < 0.001$). In the nonsurvivors, the time from hospital admission to ICU admission was significantly longer (Table 2).

Respiratory Compromise and Ventilation Support

Most of the physiological variables were greatly compromised, and the whole cohort displayed a high incidence of ARDS, extensive infiltrates on chest X-ray, and a marked alteration in oxygenation, with the need for intensive ventilation support and the use of MV adjuvants (Table 3). In nonsurvivors the incidence of ARDS was higher than in survivors (96% vs. 82%, $P < 0.001$). Death was associated with a more profound hypoxemia upon admission (Pa_{O_2}/FI_{O_2} 114 [70–188] vs. 152 [109–210], nonsurvivors vs. survivors, $P < 0.001$); lower worst Pa_{O_2}/FI_{O_2} values (80 [61–121] vs. 126 [98–164], $P < 0.001$), a higher maximal PEEP (14 ± 5 vs. 12 ± 4 cm H_2O, $P < 0.001$), and a more frequent use of salvage therapies to reverse refractory hypoxemia; such as prone positioning, recruitment maneuvers, and TGI (Table 3). One hundred fifty patients (45%) showed Pa_{O_2}/FI_{O_2} less than or equal to 100, and this characteristic was more frequent in nonsurvivors (65% vs. 28%; risk rate, 2.26; $P < 0.001$). This subgroup of severely compromised patients is further described in the online supplement (Table E3).

NIV was used in 64 patients (19%) and was associated with a better outcome. None of the patients received extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation (HFOV), or inhaled nitric oxide.

TABLE 2. DIFFERENT TIME PERIODS ELAPSING BETWEEN HOSPITAL ADMISSION, ICU ADMISSION, AND ONSET OF MECHANICAL VENTILATION

	All (*n = 337*)	Survivors (*n = 181*)	Nonsurvivors (*n = 156*)	*P* Value
Days from symptom start to hospital admission	6 [3–8]	6 [3–7]	6 [4–10]	0.13
Days from hospital admission to start of MV	1 [0–2]	0.5 [0–12]	1 [0–2]	0.33
Days from hospital to ICU admission	0 [0–2]	0 [0–1.5]	1 [0–2]	0.05

Definition of abbreviations: ICU = intensive care unit; MV = mechanical ventilation.

Data are expressed as median and interquartile ranges [IQR].

TABLE 3. PHYSIOLOGICAL AND MECHANICAL VENTILATION VARIABLES AND OUTCOME MEASURES

	All (*n = 337*)	Survivors (*n = 181*)	Nonsurvivors (*n = 156*)	*P* Value
Initiation of MV (ICU/ED/CCU)	250/69/8 (76)/(21)/(3)	137/31/6 (79)/(18)/(3)	113/32/2 (74)/(25)/(1)	ED vs. ICU 0.15 CCU vs. ICU 0.57
Lung injury score	2.62 ± 0.8	2.48 ± 0.7	2.78 ± 0.8	0.05
ARDS (AECC definition)	295/334 (88)	147/180 (82)	148/154 (96)	<0.001
Lung infiltrates on CXR (number of quadrants)	2.87 ± 1.03	2.83 ± 1.03	2.90 ± 1.03	0.68
Admission $Pa_{O_2}Fi_{O_2}$	140 [87–200]	152 [109–210]	114 [70–188]	<0.001
Lowest $Pa_{O_2}Fi_{O_2}$	107 [75–150]	126 [98–164]	80 [61–121]	<0.001
$Pa_{O_2}Fi_{O_2} \leqslant 100$	151 (45)	50 (28)	101(65)	<0.001
Admission PEEP, cm H_2O	10 ± 4	10 ± 4	11 ± 4	0.04
Admission PCO_2, mm Hg	44 ± 15	43 ± 15	45 ± 16	0.15
Maximal PEEP, cm H_2O	13 ± 5	12 ± 4	14 ± 5	<0.001
Noninvasive ventilation	64/337 (19)	43/181(24)	21/156 (13)	0.02
Tracheal gas insufflation	16/333 (5)	1/177 (0.6)	15/156+ (10)	<0.001
Recruitment maneuvers	134/333 (40)	56/177 (32)	78/156 (50)	<0.01
Prone positioning	43/334 (13)	8/178 (4)	35/156 (22)	<0.001
Use of inotropic drugs	242/336 (72)	113/181 (62)	129/155 (83)	<0.001
Hemodialysis	55/331 (17)	16/176 (9)	39/155 (25)	<0.001
Creatin-kinase, IU/L	434 [107–1,099]	255 [93–643]	754 [171–1,995]	0.03
Length of MV, d	10 [5–16]	11 [7–18]	4 [1–9]	<0.01
Length of ICU stay, d	12 [6–20]	15 [9–22]	9 [4–15]	<0.001
Length of Hospital stay, d	17 [8–29]	23 [16–36]	9 [4–17]	<0.001

Definition of abbreviations: ARDS = acute respiratory distress syndrome; AECC = American–European Consensus Conference; CCU = coronary care unit; CXR = chest X-ray film; ED = emergency department; ICU = intensive care unit; IU/L = international units per liter; MV = mechanical ventilation; PEEP = positive end-expiratory pressure.

Data are expressed as number, (%), mean ± SD, or median and interquartile ranges [IQR].

Nonpulmonary Organ Involvement

The high incidence of shock was remarkable (72% of patients were on inotropics), especially in the nonsurvivors (83% vs. 62%; $P < 0.001$). Renal failure requiring hemodialysis occurred in 17% of patients, more commonly in the nonsurvivors (25% vs. 9%, $P < 0.001$). Age, shock, and creatine-kinase levels upon admission were significantly higher in patients undergoing hemodialysis (Table 4).

Concomitant Infections

Coexistent bacterial pneumonia on admission was diagnosed in 80/325 patients (25%), with the proportions being similar between confirmed and nonconfirmed cases (Table 5). Within the entire group, 28 patients (9%) had pneumonia caused by *S. pneumoniae* (6% in the survivors vs. 11% in the nonsurvivors, $P = 0.11$). Ventilator-associated pneumonia developed in 84/325 patients (26%); *Acinetobacter baumanii* was the most frequently isolated microorganism (n = 35), followed by *Pseudomona aeruginosa* (n = 22).

Outcomes and Predictors of Mortality

One hundred fifty-six patients died (46%; Table 1 and Figure 1); 62% were male, and 67% had a previous medical condition, of which habitual smoking and obesity were the most frequent. Patients with immunosuppression died earlier (Figure 1). Mortality was distributed evenly across all age categories, without significant differences among them (Figure E2). Logistic-regression analysis identified the APACHE II score, the lowest Pa_{O_2}/Fi_{O_2}, the use of inotropics, hemodialysis, prone positioning, and concomitant pneumococcal pneumonia as independent predictors of hospital mortality (Table 6). The predictive model showed good calibration (Hosmer-Lemeshow test = 10.85; $P = 0.21$) and discrimination (area under ROC curve = 0.81).

Comparison with Other Studies

A systematic comparison of epidemiological, clinical, and outcome data between this study and others (11–17) is shown in Table E4. The relationship between outcome and the period elapsing from symptom onset to hospital admission for our study and other studies (11–17) is included in Table E5.

DISCUSSION

We report on a large cohort of critically ill patients admitted to 35 ICUs of Argentina with suspected, probable, or confirmed 2009 influenza A (H1N1) and with acute respiratory failure requiring MV. These severely compromised patients were typically middle-aged adults, predominantly male, and presented with great physiological deterioration, as evidenced by high APACHE II score, bilateral lung infiltrates on chest X-ray, and deep hypoxemia. Nonpulmonary organ dysfunctions requiring extracorporeal support, such as shock and renal failure, were frequent; and mortality was correspondingly high. This evolution occurred rapidly after about 1 week of ILI symptoms, a pattern that seems to be a hallmark of severe disease observed also in other studies (11, 12).

With respect to the patients' characteristics, 74% were between 25 and 64 years old, but 15% were older than 65. In contrast to the usual target population of seasonal influenza, in which children and adults aged 65 years or more are preferentially affected (18, 19), a lower mean age has been a consistent

TABLE 4. CHARACTERISTICS OF PATIENTS REQUIRING RENAL SUPPORT

	No hemodialysis (*n = 276*)	Hemodialysis (*n = 55*)	*P* Value
Age	45.9 ± 17,1	51.3 ± 15,4	0.03
Use of inotropic drugs	191 (69)	49 (89)	0.003
CK (IU/L) on Day 1*	265 [94–765]	927 [144–1,856]	0.016

Definition of abbreviations: CK = creatine kinase levels; IU/L = international units per liter.

Data are expressed as number, (%), mean ± SD, or median and interquartile ranges [IQR].

* Data of 98 patients.

TABLE 5. COEXISTENT RESPIRATORY INFECTIONS

	All	Survivors	Nonsurvivors	*P* Value	Incidence in Confirmed Cases	Incidence in Nonconfirmed Cases	*P* Value
n	325	175	150		132	190	
Pneumonia on admission	80 (25)	40 (23)	40 (27)	0.43	37 (28)	43 (22)	0.19
VAP in the evolution	84 (26)	46 (26)	38 (25)	0.78	33 (25)	51 (27)	0.77

Definition of abbreviation: VAP = ventilator-associated pneumonia.
Data are expressed as n (%).

finding in populations affected by this 2009 influenza A (H1N1) virus (4, 5, 11–17). Still, the mortality was comparable across all age groups (Figure E2).

Similar to what has been described in other reports, nearly two-thirds of the patients had previous medical conditions (13, 14, 16); and, as in seasonal influenza, habitual smoking and chronic lung disease were the most frequent. The COPD prevalence of 18%, however, was not higher than in the general population for the region (20). Obesity, a novel risk factor for influenza A described during the 2009 pandemic (21), occurred in 24% of the patients and was comparable to the prevalence of this condition in Argentina (22). Thus, obesity and chronic respiratory disease were the two main risk factors for this novel influenza virus, which has been a consistent report (11–17; Table E5). Immunosuppression was also frequent, and mortality occurred earlier in this subgroup. Finally, 36% of the patients were in a previous state of good health. The prevalence of pregnancy (7%) (11–17, 23) was higher than in the general population (1.7% for Argentina; 24). Pregnancy is a well-known risk factor for seasonal influenza and had caused significant morbidity and mortality during past epidemics and pandemics (25, 26). Notably, none of the pregnant women had been previously vaccinated for seasonal influenza.

Severe respiratory involvement was a key feature of patients infected with the 2009 influenza A (H1N1) virus and admitted to the ICU. MV was initiated generally during the first day of hospital admission, mostly in the ICU. In 24% of the patients, intubation occurred in other hospital locations, such as the ED or the CCU, reflecting the acuity of the condition on admission along with the degree of congestion of the acute-care facilities that was so frequent during the outbreak. Extensive radiological lung infiltrates and profound hypoxemia requiring high levels of ventilation support were the rule and were more prominent in nonsurvivors. In contrast to what is usually described in epidemiological series of ARDS (27, 28), in which multiple organ dysfunction is the main cause of death, in ARDS caused by the 2009 influenza A (H1N1) virus, mortality was also highly associated with refractory hypoxemia. This novel virus elicits a more pronounced low-tract respiratory disease in mice, ferrets, and primates than do seasonal H1N1 viruses (29, 30). In addition, necropsy studies revealed diffuse alveolar damage, necrotizing bronchiolitis, intense alveolar hemorrhage, and evidence of lung abnormal immune response (31).

NIV was used in 19% of patients at any time, in contradiction to recommendations regarding possible aerosolization of viral particles (32, 33), and was associated with a better outcome—possibly because attending physicians selected NIV use for the less hypoxemic patients. NIV utilization has also been reported in other series (11, 12, 16).

Nonpulmonary organ involvement was unusually high. For example, inotropics were used in 72% of the patients—compared with 32, 58.6, 62.5 (11, 12, 16) and 69% in nonsurvivors in whom autopsy was performed (31)—or not used at all (13, 14) (Table E4). Another striking finding was the high frequency of acute kidney injury requiring hemodialysis (17% of the patients). Three studies described this complication (16, 17, 31)—one reporting a high mortality (17) and another being an autopsy series from Brazil (31)—although less severe forms of renal dysfunction have also been described (12; Table E4). Aside from shock, another possible concurrent cause of renal failure is rhabdomyolysis, a complication that has been described in seasonal influenza mostly in children (34). Accordingly, in our patients requiring hemodialysis creatine-kinase levels were significantly increased. Up to the present moment, there is no evidence of direct viral damage to the kidney (31, 35).

Bacterial coinfection on admission has long since been reported in seasonal influenza and is one of the presumed

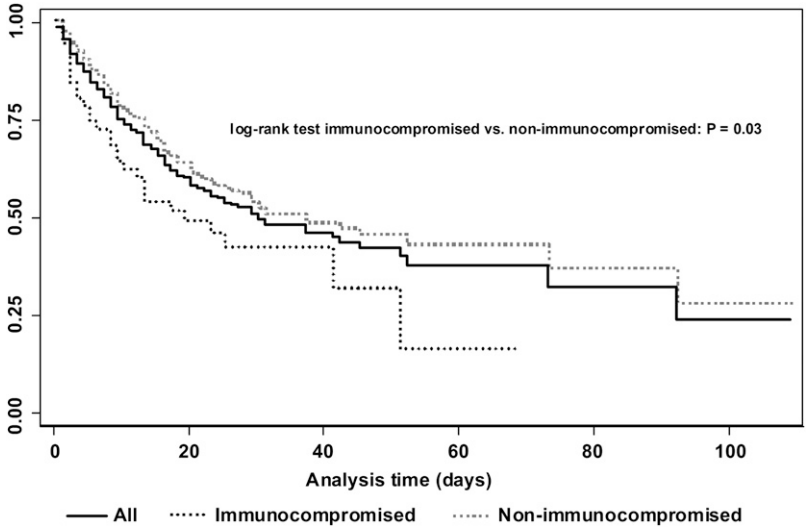

Figure 1. Survival curve of patients with 2009 Influenza A (H1N1) for the entire population (*continuous line*), for immunocompromised patients (*lower dotted line*), and for non-immunocompromised patients (*upper dotted line*).

TABLE 6. INDEPENDENT PREDICTORS OF HOSPITAL MORTALITY

	Odds Ratio	*P* Value	95% Confidence Interval
APACHE II	1.08*	<0.001	1.03–1.12
Lowest $Pa_{O_2}Fl_{O_2}$	0.98†	<0.001	0.98–0.99
Use of inotropic drugs	2.32	0.01	1.23–4.38
Hemodialysis	2.85	<0.01	1.30–6.25
Prone positioning	4.07	<0.01	1.55–10.68
Coinfection with *S. pneumoniae* at admission	2.72	0.04	1.05–7.06

Definition of abbreviation: APACHE = Acute Physiology and Chronic Health Evaluation.

* Per point APACHE II.

† Per point $Pa_{O_2}Fl_{O_2}$.

causes of death in pandemics (31, 35–37). A synergistic interaction between bacteria and the influenza viruses has been described, involving an augmented viral replication and an increased ability to bind and invade bacteria, especially *S. pneumoniae*, resulting in a globally increased inflammatory response (31, 35, 38). In recent years, this complication is apparently rising (39). We observed a 25% incidence of bacterial pneumonia on admission, and this proportion was equal in both survivors and nonsurvivors. Coinfection with *S. pneumoniae*, however, worsened the prognosis, despite concurrent antibiotic treatment on admission.

The mortality figure of 46% observed here is high, but we chose to focus on only the subgroup comprising the sickest adult patients (40), those on MV. Reported mortalities are of 14.3% (11, 13), 21% (41), 25% (16), and 41.4% (12). Most series report on general ICU mortality at 28 days (11, 12), whether patients were or were not on MV, and on adult and pediatric patients together (Table E4). This last group has a better prognosis (11). The standard consideration of 28-day mortality (12, 11) could also cause a transient underestimation of deaths (11). By contrast, we followed up patients all the way to either death or discharge. In a U.S. cohort of 272 hospitalized patients (14), only 7% of the total died; but, of the 67 patients that had been admitted to the ICU, 19 out of the 42 on MV died (45%). The distribution of different organ failures among diverse populations could explain these differences: For example, acute kidney injury—it was very frequent in our study—is a well-known risk factor for death in the critically ill (42). Mortality rates for combined acute kidney injury and acute lung injury might exceed 80% in critically ill patients (43). ECMO, a rescue therapy not currently available in Argentina, has been associated with a better outcome (40), which might also explain these results.

In the present study, the period from symptom onset to hospital admission was about 6 (3–8) days, similar to the Mexican study (6 [4–8]) (12), but longer than the Australian/New Zealand and Canadian reports (4 [2–7] days for both) (11, 13). Longer symptom onset–hospital admission periods were associated with increasing mortality (Table E5). Differences in the accessibility to healthcare facilities along with differing perceptions of disease severity on the part of both the patients and the attending physicians could account for these discrepancies. Unfortunately, since our study was not designed to assess the relationship between the time of disease onset and the start of oseltamivir treatment, we cannot discard the possibility that the length of this interval could be a yet-undetermined factor affecting outcome.

The subgroup of pregnant or postpartum patients also displayed a high mortality: 10 out of these 22 patients died (45%), consistent with a recent study from California (44) where, of 94 pregnant or postpartum patients with 2009 influenza A (H1N1), 22 were admitted to the ICU, 16 required MV, and 8 died (50%), once again underscoring the increased risk of severe disease within this subpopulation (11, 13).

Finally, by the use of logistic-regression analysis, we identified APACHE II, the lowest Pa_{O_2}/Fi_{O_2}, prone positioning, use of inotropics, hemodialysis, and coinfection with *S. pneumoniae* as independent predictors of mortality. Thus, there is an association of global severity of disease on admission with worsening oxygenation and nonpulmonary organ failures affecting outcome. It is striking that pneumococcal infection, long since considered the cause of death in past pandemics, is also prognostic in this model.

The strength of this study lies in that it involves the second largest cohort of adult mechanically ventilated patients with the 2009 influenza A (H1N1), with these cases described and analyzed in great detail. In addition, this is the first study identifying independent predictors of mortality in the most severely compromised subgroup of patients: those on MV. Other complications, such as shock and renal compromise, are also characterized. The information was collected in a standardized form along with the ongoing pandemic, so that most data were recorded prospectively.

This study also has its limitations: the high frequency of renal failure requiring hemodialysis might be a regional characteristic; so findings might not be generalizable to other populations. No data on the timing of oseltamivir use with respect to symptom onset was registered. Not all the patients were confirmed cases by RT-PCR analysis; but since there were no differences in mortality between confirmed and nonconfirmed cases, both categories were included. In this regard, other studies have used a similar approach (12). Furthermore, difficulties in the availability of confirmatory diagnoses once a pandemic is in progress have been well described (11).

In conclusion, this study highlights important points deserving consideration for future health-resource planning in similar scenarios: First, late admission to the ICU is associated with a greater likelihood of nonsurvival; so planning for an increase in ICU beds in advance seems warranted, especially when a great volume of patients is anticipated (45, 46). We, as others (13), have registered that the peak in admissions to the ICU is to be expected 4 to 6 weeks after the first case. Second, limited diagnostic resources should be redirected to the most severe cases to improve general management and decrease uncertainty in the healthcare workers and in patients and their relatives. Third, the identification of key risk factors will aid in health-resource preparedness in general and in vaccination planning in particular. Fourth, efforts should be targeted at improving vaccination against seasonal influenza in pregnant women, since they constitute a subpopulation at particular risk for all types of influenza A. Finally, the need for sufficient equipment appropriated for advanced ventilation support should be considered, given that mortality was highly associated with refractory hypoxemia.

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