

TITLE:

Lung Function and Organ Dysfunctions in 178 Patients Requiring Mechanical Ventilation During The 2009 Influenza A (H1N1) Pandemic

ABSTRACT:

INTRODUCTION: Most cases of the 2009 influenza A (H1N1) infection are self-limited, but occasionally the disease evolves to a severe condition needing hospitalization. Here we describe the evolution of the respiratory compromise, ventilatory management and laboratory variables of patients with diffuse viral pneumonitis caused by pandemic 2009 influenza A (H1N1) admitted to the ICU. METHOD: This was a multicenter, prospective inception cohort study including adult patients with acute respiratory failure requiring mechanical ventilation (MV) admitted to 20 ICUs in Argentina between June and September of 2009 during the influenza A (H1N1) pandemic. In a standard case-report form, we collected epidemiological characteristics, results of real-time reverse-transcriptase--polymerase-chain-reaction viral diagnostic tests, oxygenation variables, acid-base status, respiratory mechanics, ventilation management and laboratory tests. Variables were recorded on ICU admission and at days 3, 7 and 10. RESULTS: During the study period 178 patients with diffuse viral pneumonitis requiring MV were admitted. They were 44 ± 15 years of age, with Acute Physiology And Chronic Health Evaluation II (APACHE II) scores of 18 ± 7 , and most frequent comorbidities were obesity (26%), previous respiratory disease (24%) and immunosuppression (16%). Non-invasive ventilation (NIV) was applied in 49 (28%) patients on admission, but 94% were later intubated. Acute respiratory distress syndrome (ARDS) was present throughout the entire ICU stay in the whole group (mean $\text{PaO}_2/\text{FIO}_2$ 170 ± 25). Tidal volumes used were 7.8 to 8.1 ml/kg (ideal body weight), plateau pressures always remained < 30 cmH₂O, without differences between survivors and non-survivors; and mean positive end-expiratory pressure (PEEP) levels used were between 8 to 12 cm H₂O. Rescue therapies, like recruitment maneuvers (8 to 35%), prone positioning (12 to 24%) and tracheal gas insufflation (3%) were frequently applied. At all time points, pH, platelet count, lactate dehydrogenase assay (LDH) and Sequential Organ Failure Assessment (SOFA) differed significantly between survivors and non-survivors. Lack of recovery of platelet count and persistence of leukocytosis were characteristic of non-survivors. Mortality was high (46%); and length of MV was 10 (6 to 17) days. CONCLUSIONS: These patients had severe, hypoxemic respiratory failure compatible with ARDS that persisted over time, frequently requiring rescue therapies to support oxygenation. NIV use is not warranted, given its high failure rate. Death and evolution to prolonged mechanical ventilation were common outcomes. Persistence of thrombocytopenia, acidosis and leukocytosis, and high LDH levels found in non-survivors during the course of the disease might be novel prognostic findings.

Introduction:

On April 2009, a novel influenza A (H1N1) virus emerged in Mexico and spread rapidly across the world [1,2]. As of 17 June 2010, more than 214 countries had reported confirmed cases of infection with pandemic 2009 influenza A (H1N1) virus, including at least 18,156 deaths [3]. Unlike seasonal influenza, in which hospitalizations occur among patients younger than 2 and older than 65 years, or in those with underlying diseases [4], this novel virus affected otherwise healthy young and middle-aged adults and obese individuals [2,5]. Patients with previous respiratory disease, immunocompromised hosts and pregnant women were affected as frequently as with seasonal influenza [6-15]. Although a mild form of the disease was prevalent, it soon became evident that the 2009 influenza A (H1N1) virus could also provoke severe, acute respiratory failure requiring admission to the intensive care unit (ICU) for mechanical ventilation [16], which was reflected in the severe pathological injury found at autopsy [17].

The Argentinian population was greatly affected during the pandemic, with a total of 1,390,566 cases of influenza-like illness requiring 14,034 hospitalizations. Of the 11,746 confirmed cases of patients infected with the new strain, 617 died [18]. This represents a death rate per infection of 4.3% in hospitalized cases; an intermediate figure compared to 3.6% in Brazil, 1.2% in Chile, and approximately 6% in Uruguay, Colombia and Venezuela [19]. It should be noted that these numbers reflect great uncertainty, particularly with regard to case diagnosis. Lack of testing of mild disease and difficulties due to laboratory overload have also been well described [15,20]. These general problems have been acknowledged by experts [21].

The severity of disease was rapidly perceived by health authorities and scientific societies. Hence, a committee of experts of the Argentinian Society of Intensive Care Medicine decided to focus on the most acutely ill patients: those presenting with diffuse viral pneumonitis requiring mechanical ventilation. They designed an epidemiological study, recently-published, to determine risk factors and outcomes [15]; this is one of many series up to the present that have described epidemiological and clinical aspects of the 2009 influenza A (H1N1) pandemic [6-15]. There remains, however, a paucity of data published on physiological evolution during ICU stay [22]. This present study, concurrently planned with the first by the same committee of experts, thus aims to provide such information. Our objectives were: first, to characterize alterations of oxygenation, respiratory mechanics and the use of mechanical ventilation; second, to explore compliance with protective lung ventilation; and, finally, to assess the evolution of laboratory findings and organ dysfunctions throughout the course of the disease.

Statistical analysis :: Materials and methods:

Statistical analysis was performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed for the entire population; for the subgroups of survivors vs. non-survivors; and for patients receiving NIV on admission vs. those who did not. Descriptive statistics used were: mean \pm standard deviations (SD) and median and 25-75% interquartile ranges (IQR) for continuous data of normal and non-normal distribution, respectively; and percentages for categorical data.

Differences between subgroups were analyzed with unpaired t test, Mann-Whitney U test, and Chi-square tests, as appropriate. A P-value of $< .05$ was considered statistically significant. A Kaplan-Meier curve was constructed to evaluate survival over the follow-up period.

Over time, normally distributed data were analyzed with two-way repeated measures of ANOVA.

At the pre-specified time points, differences within the entire group and subgroups, and between subgroups, were tested using paired and unpaired t tests, respectively.

In non-normally distributed data, differences over time within the entire group and the subgroups were analyzed with Friedman's and Wilcoxon tests. Comparisons between subgroups at the pre-specified time points were tested with Mann-Whitney U test. The Bonferroni correction was used to adjustments for multiple comparisons.

The local Institutional Review Boards waived the need for informed consent, given the general lack of knowledge on the clinical and outcome characteristics of the ongoing pandemic and to the non-interventional study design.

General characteristics (Table 1T1table) :: Results:

Between 6 June and 28 August 2009, the SATI's online Registry included 337 patients admitted to 35 ICUs with confirmed/probable/possible diffuse viral pneumonitis caused by influenza A (H1N1), with acute respiratory failure requiring MV (14). Of these, 178 consecutive patients admitted to 20 ICUs were followed over time, and are presented in this study. To address any potential concern that unconfirmed cases could belong to a different population of patients, we performed a sensitivity analysis of clinical and outcome characteristics data after exclusion of these patients. The results of this analysis did not differ from those of the primary assessments, so the 178 patients are considered for evaluation.

Briefly, patients were middle-aged, with no gender preponderance; they had a history of symptoms of nearly one-week duration and were ventilated at 1 [0 to -2] day after hospital admission. Pre-existent respiratory diseases, obesity, and diseases causing immunosuppression were the most frequent comorbid conditions; and prevalence of pregnancy was higher than in the general population, as expected [25]. Non-survivors were sicker on admission; duration of previous symptoms was longer; and organ failures were more severe. Obesity and immunosuppression were significantly more frequent as predisposing conditions. Ninety-three patients survived (52%) (See Figure 1).

Clinical and mechanical ventilation-related variables (Table 2T2table) :: Results:

During the study period, the entire group had Vt values between 7.8 to 8.1 ml/kg of IBW, with plateau pressures remaining always < 30 cmH₂O. Non-survivors displayed a trend towards lower Vt and higher plateau pressures, which differed significantly from survivors only at Day 7. Intermediate PEEP levels were used, and decreased in survivors from Day 3 onwards. Driving pressures were similar over time in all patients; only at admission did non-survivors exhibit higher values.

PaO₂/FIO₂ increased significantly over time in all patients and in survivors. It remained, however, < 200 in the whole group throughout the entire ICU stay due to non-survivor values. Non-survivors displayed significantly lower PaO₂/FIO₂ at all time points.

Lung infiltrates (in quadrants) peaked at day 3 (3.1 ± 1.0 vs. 2.9 ± 1 at Day 0, $P < 0.01$) and then decreased during the study in the entire group, especially at Day 10 (2.8 ± 1.1 , $P < 0.83$ vs. Day 0), which reflected the improvement in survivors (3.1 ± 1.0 at Day 3 vs. 2.9 ± 1.0 at Day 10, $P < 0.01$).

In Figure 2, the utilization of ventilation modes and rescue therapies in the entire group are shown. Briefly, PCV use equaled VCV at Day 10, preceded by deterioration in oxygenation and respiratory mechanics: PaO₂/FIO₂ 78 ± 24 vs. 128 ± 33 , ($P = 0.03$); PaCO₂ 44 ± 4 vs. 35 ± 3 mmHg ($P = 0.04$); pH 7.29 ± 0.03 vs. 7.39 ± 0.05 ($P = 0.05$), and plateau pressures of 30 ± 2 vs. 25 ± 3 cmH₂O ($P = 0.03$). Recruitment maneuvers became significantly more common in non-survivors at Day 3 (46%, vs. 29% in survivors; $P = 0.03$), as did prone positioning (24%, vs. 14%; $P = 0.001$). After that, only prone positioning remained significantly more used in non-survivors (at Day 7: 38%; vs. 14%, $P = 0.004$; and at Day 10: 25%; vs. 5%, $P = 0.02$). Six patients received tracheal gas insufflation; only one survived. Neuromuscular blockers were prescribed in 18% of patients on admission; and their use was subsequently more frequent in non-survivors (Day 3: 14% vs. 8%, $P = 0.02$; and Day 7: 14% vs. 8%, $P = 0.04$).

The main causes of death were refractory hypoxemia (64%); followed by multiorgan dysfunction syndrome (15%) and shock (10%). Prolonged mechanical ventilation and long ICU and hospital stays were frequent (Table 1). Tracheostomy was performed in 29 patients (16%) at Day 14 [11-21].

Acid-base variables and fluid balance (Table 3T3table) ::: Results:

Arterial pH increased over time in the whole cohort and in both subgroups, perhaps secondary to general resuscitation measures. Despite this, non-survivors displayed significantly lower pH at all time points, owing to changes in base excess on Days 0 and 3, and to pCO₂ elevations thereafter. Respiratory rates remained unchanged, only increasing at Day 10 in non-survivors; nevertheless, this corresponded to the highest pCO₂ values, indicating the more severe respiratory compromise. Bicarbonate paralleled pH behavior.

Changes in fluid balance did not show clear trends: only at Day 10 they decreased significantly, expressing survivors' behavior.

Use of noninvasive ventilation (Tables 4T4table and 5T5table) ::: Results:

Forty-nine patients (28%) underwent a trial of NIV on admission; they were significantly less ill and had a lower incidence of immunosuppression. Oxygenation and outcome variables were similar to those of patients not receiving NIV.

Sixty-one percent of patients ($n = 30$) receiving NIV survived; duration of NIV was of 8 (2 to 18) hours. There were no differences between survivors and non-survivors in the duration of the procedure, or in the type of interface or respirator used. Of note, most patients on NIV (46 out of 49; 94%) had to be intubated and ventilated invasively for hypoxemic failure. Characteristics associated to NIV success/failure are shown in Table 5.

NIV was also used for treating post-extubation respiratory failure in 12 of 178 patients (7%), with success (reintubation not needed) in 8 cases (66%).

Blood chemistry and organ failures ::: Results:

The most consistent changes over time were found in platelet count, which increased significantly in the whole cohort ($P < 0.000$ for Days 3, 7 and 10 vs. Day 0), secondary to elevations in survivors. At all time points, platelets differed between survivors and non-survivors. Conversely, white blood cell count showed a progressive increase in the whole group ($P < 0.000$ for Days 7 and 10 vs. Day 0), due to elevations in non-survivors.

Creatine-kinase and markers of liver injury (alanine/aspartate aminotransferases, serum bilirubin; not shown) were mildly elevated and displayed no substantial changes. On the contrary, lactate-dehydrogenase levels were significantly higher in non-survivors throughout the study. Creatinine levels were stable over the period, but were significantly higher in non-survivors on Days 0 and 3. Finally, SOFA score diminished over time in all patients ($P < 0.000$ for Days 7 and 10 vs. Day 0), as a result of the decrease in survivors. SOFA was significantly lower in survivors throughout the study.

In Figure 3, the differences between survivors and non-survivors are displayed.

Discussion:

We report on a large, prospective cohort of 2009 influenza A (H1N1) patients that were mechanically ventilated for acute respiratory failure due to diffuse pneumonitis during the pandemic in Argentina. Though most were middle-aged, previously healthy adults, patients with preexistent lung disease, immunosuppression, obesity and pregnancy were also affected. Mortality was high and evolution to chronic critical illness was common, as shown by prolonged mechanical ventilation, high needs of tracheostomy, and lengthened ICU and hospital stays. Patients had characteristically a history of protracted symptoms and displayed severe compromise of oxygenation compatible with ARDS throughout the study period, which only improved in survivors. At all time points, PaO₂/FIO₂ differed significantly between survivors and non-survivors, requiring higher FIO₂ and PEEP in this last subgroup. Yet the levels of applied PEEP were only in the intermediate range, similar to mean values of 8.7 cmH₂O of PEEP in an international study on mechanical ventilation [26], which may explain the relatively high FIO₂ used in our study. Driving pressures were similar in both subgroups most of the time, suggesting an intention to limit alveolar excursion as part of a protective strategy.

It is striking that, as has been described in similar studies on mechanical ventilation performed during the 2009 influenza A (H1N1) pandemic [6,7], tidal volumes used were between 7.5 and 8.3 ml/kg IBW, certainly higher than the 6 ml/kg demonstrated as being lung-protective [27]. Indeed, barriers to implementing low-tidal volume have been identified and might explain physician behavior [28]. Despite this, plateau pressures did remain below 30 cmH₂O [29], indicating that lung compliance might have been preserved. Perhaps clinicians focused on plateau pressures rather than on tidal volumes [30] since it still remains unclear which should be limited to avoid ventilator-induced lung injury [31]. We, like others [6,7,32,33], could not find differences in utilized tidal volumes between survivors and non-survivors. Even so, non-survivors tended to display lower values, probably reflecting physician efforts to intensify protective ventilation strategies in the most severely compromised. Some researchers [34,35] have suggested that allowing higher tidal volumes in a population of young and previously healthy patients with strong ventilatory drive might reveal an attempt to restrain heavy sedation and neuromuscular blocker use.

Notwithstanding this, we believe that these findings may also represent clinicians' inadequate prescription, as described in other scenarios [36].

Not unexpectedly, VCV was the most common ventilator mode used. PCV use increased throughout the study period, peaking at Day 10. This is in contrast with the recently identified trend towards decreased PCV utilization. Transition to PCV mode was associated with preceding physiological worsening, so clinicians might have perceived PCV utilization as part of a global lung-protective strategy [37].

Refractory hypoxemia was the main cause of death. As in other studies [6,7,11], rescue therapies were frequently applied, with utilization highest 72 hours after admission. Recruitment maneuvers and prone positioning were the primary adjuvants utilized; ECMO and HFOV are currently not available in Argentina. A prolonged mechanical ventilation course was frequent as reported elsewhere [6].

NIV was the first ventilation approach in 28% of cases, with 94% later requiring invasive ventilation, as has been documented in other studies [6,7,11]. These common experiences should caution against delaying proper ventilatory support in this group, given that rapid deterioration is common. A recent meta-analysis suggests that NIV does not decrease the need for intubation, so evidence to support its use in severe ARDS is questionable [38]. In our study, improved outcomes with NIV could be due to milder disease, evidenced by APACHE II. The small number of patients that were not intubated precludes a statistical analysis; however, they were younger, with less severe disease and better oxygenation.

Significant changes in fluid balance were late and reflected changes in survivors. Negative fluid balances could never be obtained, perhaps suggesting a continuing need for hemodynamic support: 72% of patients presented with shock [14]. On the whole, fluid balances remained between those achieved by "liberal" and "conservative" strategies of the fluids and catheters treatment trial, depending on the day evaluated [39]. Thus far, it is not clear whether the negative fluid balance has a causal role in improving outcome in ALI/ARDS, or if it simply expresses the global recovery of patients.

Another important finding was that arterial pH consistently and significantly differed between survivors and non-survivors, as described elsewhere [40,41]. During the first 72 hours acidosis had a major metabolic component, likely as a sign of hemodynamic impairment. After the first week, respiratory acidosis ensued, indicating either the effects of protective ventilation, or merely

deterioration due to progressive shunt, profound ventilation/perfusion mismatch and increased deadspace.

With respect to blood chemistry, the usual findings of thrombocytopenia, leukocytosis and mildly elevated creatine-kinase blood levels were present [21,42]. Regrettably, the lymphocyte count was not recorded. In viral infections, thrombocytopenia occurred frequently. Although the mechanisms by which the 2009 influenza A (H1N1) virus causes thrombocytopenia are unknown, its lack of resolution is a marker of poor prognosis. Both leukocytosis and leucopenia have been found in hospitalized patients with 2009 influenza A (H1N1) [2,43]; in our study, persistent leukocytosis was associated with increased mortality. LDH elevations have been previously described in fatal cases [2], which corresponded to our finding of higher LDH levels in non-survivors at all time points. Such elevations have also been reported in seasonal influenza [44]. In experimental studies, increased LDH is a marker of human fetal membrane cell apoptosis induced by influenza virus [45]. Finally, multiorgan failure was frequent, and predictably more severe in non-survivors. This study has several strengths: first, the clinical characteristics and time course of pandemic 2009 influenza A (H1N1) are thoroughly described and analyzed. Second, data were collected prospectively in consecutive patients and with a standardized case-reporting form, representing a large, nationwide cohort. Third, temporal patterns of mechanical ventilation use, acid-base and blood chemistry variables, as well as fluid balance and organ failures, are carefully analyzed. Prognostic implications are highlighted. Finally, we present the largest experience with NIV use during the pandemic.

Study limitations include the focus on mechanically ventilated patients, excluding less severe cases also admitted to the ICU. Many cases could not be confirmed because laboratories were overwhelmed with clinical samples, which is also described elsewhere [7,14]. Data about transmission to healthcare workers were not recorded, especially regarding NIV. Currently, most information about its use during an epidemic relies upon expert opinion [46].

Conclusions:

In 178 patients with diffuse viral pneumonitis caused by the 2009 influenza A (H1N1) virus admitted to the ICU and followed over time, ARDS was the rule, requiring high ventilation support and frequent use of rescue therapies. Death, organ failures, and evolution to prolonged mechanical ventilation were common. In most cases, noninvasive ventilation failed to prevent endotracheal intubation. Finally, elevated LDH levels, lack of recovery of platelet count and persistent acidosis and leukocytosis in non-survivors behaved as prognostic findings.

Key messages:

- In 2009 influenza A (H1N1) patients, hospital admission with prompt indication of mechanical ventilation - a marker of severe disease - was associated with a history of symptoms of nearly one-week duration.
- An initial NIV trial was not effective to avoid intubation in most patients; thus, this ventilation approach should likely be discarded in this setting.
- Mortality and morbidity were frequent: death was common and was mainly caused by persistent, refractory hypoxemia. Prolonged mechanical ventilation and ICU and hospital stays were typical.
- pH, platelet count, LDH and SOFA differed significantly between survivors and non-survivors over time. Lack of recovery of platelet count and persistence of leukocytosis might be markers of poor prognosis.
- Every effort should be done to increase adherence to protective ventilation in the real world.

Abbreviations:

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; BMI: body mass index; CXR: plain chest X-ray film; IBW: ideal body weight; ICU: Intensive Care Unit; LDH: lactate dehydrogenase assay; LOS: length of stay; MV: mechanical ventilation; NIV: non-invasive ventilation; PaO₂/FIO₂: relation between patient arterial pO₂ and inspired oxygen fraction used; PCV: pressure-controlled ventilation; PEEP: positive end-expiratory pressure; PSV: pressure support ventilation; RR: respiratory rate; RT-PCR: real-time reverse-transcriptase--polymerase-chain-reaction; SATI: Argentinian Society of Intensive Care; SOFA: Sequential Organ Failure Assessment; VCV: volume-controlled ventilation; Vt: tidal volume.

Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

FGR conceived and coordinated the study. FGR and EE drafted the manuscript and performed the statistical analysis. FGR, FV, RV, AG, DV and GC participated in the design of the study. FGR, EE, FV, RV, LA, DP, PV, MB, CO, JA, FS, AG, PEG, MD, AZ, MQ, AC, JO, DV, MEG, GC and the rest of the members of the Registry performed the acquisition of data. All authors read and approved the final manuscript.