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## Influenza A (H1N1) patients admitted to intensive care units during the 2009 pandemics: clinical features and outcomes

*Apresentação clínica e evolução de pacientes com infecção por Influenza A (H1N1) que necessitaram de terapia intensiva durante a pandemia de 2009*

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### ABSTRACT

**Objectives:** To describe the clinical features and outcomes of patients admitted with influenza A (H1N1) infection in two private hospitals' intensive care units in São Paulo, Brazil, during the 2009 pandemics.

**Methods:** A retrospective cohort study was conducted to evaluate demographic data, initial clinical presentation, prognostic scores [Simplified Acute Physiology Score (SAPS) 3 and Sequential Organ Failure Assessment (SOFA)], comorbidities, outcomes and treatment of patients with confirmed pandemic influenza diagnosis from July to September 2009.

**Results:** 22 patients were admitted. Median age was 30 (25-43.5) years. Median SAPS 3 and SOFA were 42 (37-49) and 2 (1-3.5), respectively. Comorbidities were common (45.4%), especially obesity (22.7%). Two (9.1%) patients were pregnant. Five (22.7%) patients required in-

sive mechanical ventilation, with high positive end expiratory pressures (median of 16 cmH<sub>2</sub>O, interquartile range 10-25cmH<sub>2</sub>O). There was a 50% incidence of non-invasive ventilation failure. Most (77.2%) of patients were treated with oseltamivir. Hospital mortality was 4.5%. Initial SAPS 3, SOFA and PaO<sub>2</sub>/FiO<sub>2</sub> ratio were associated with mechanical ventilation requirement (p<0.01).

**Conclusions:** Pandemic influenza infection mainly affected young and obese patients. In this study, patients were less severe than those previously described, what explains our low mortality and mechanical ventilation needs. However, high positive end expiratory pressures were required for mechanically ventilated patients.

**Keywords:** Influenza A virus, H1N1 subtype; Diseases outbreaks; Intensive care units; Respiration, artificial

### INTRODUCTION

In April 2009, an acute respiratory disease epidemics started in Mexico. At the same period, two influenza A (H1N1) cases were described in the United States.<sup>(1)</sup> The disease spread quickly, and on June 11, 2009, the World Health Organization raises the pandemics alert to 6 (highest level), with interpersonal transmission evidenced in at least two continents.

This virus subtype occurred due to a human, swine and avian virus gene recombination, and given the lack of prior immunity to a large population, it was quickly disseminated.<sup>(2)</sup>

In Brazil, the dissemination was officially confirmed on July 16, 2009. In August 21, 2009, Brazil accumulated 34,506 severe acute respiratory di-

sease cases. Of these, 5,457 were laboratory confirmed secondary to pandemic influenza A (H1N1) infection (2009);<sup>(3)</sup> however, the total number of cases was probably higher, as, because of the epidemics progression, the Brazilian Ministry of Health ordered only severe cases to be tested.

The first descriptions suggested that the virus affected mainly young people,<sup>(4)</sup> and as a consequence of its broad dissemination, high absolute severe cases numbers were recorded. Mortality rate was variable on the several articles reporting patients requiring intensive care unit (ICU) admission.<sup>(5-12)</sup> So far, only one cases series of patients admitted to ICU was published in Brazil,<sup>(11)</sup> with some similarities with the Mexican experience,<sup>(8)</sup> nevertheless the outcomes were different from other countries.

This study was aimed to describe the clinical features and outcomes of patients admitted to two private hospitals' intensive care units in São Paulo, Brazil, from July 01 to September 30, 2009.

## METHODS

This was a historical cohort study, including all patients aged 18 years or more admitted to both intensive care units with a respiratory syndrome and confirmed pandemic (2009) influenza A (H1N1) infection. The study was approved and authorized by the hospitals' ethics committees. As no individual data was exposed and all data were obtained from medical charts, no informed consent was required.

### Data collection

The search for cases was conducted based on the hospitals' infection control committees (CCIH) records, where all suspected and confirmed influenza A (H1N1) cases were recorded during this period. Additionally, both ICUs have databases for mortality analyses on which patients' diagnoses are recorded. The information on confirmed cases admitted to the ICU came from these databases.

The following data were collected from medical charts:

1. Demographics: age, gender, body mass index (BMI);
2. Comorbidities: asthma, chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus (DM), obesity (defined as BMI > 30 kg/m<sup>2</sup>), immunosuppression [chemotherapy, radiotherapy, systemic corticosteroid use above 5 mg prednisolone

(or equivalent) day], metastatic cancer, hematological cancer, acquired immunodeficiency syndrome (AIDS), functional class IV heart failure (FC IV HF), pregnancy (and pregnancy age);

3. Initial presentation: symptoms and its duration before hospital admission, partial oxygen pressure/inspired oxygen fraction ratio (PaO<sub>2</sub>/FiO<sub>2</sub>), severity scores [Simplified Acute Physiology Score (SAPS) 3 and Sequential Organ Failure Assessment (SOFA)];

4. Treatment: mechanical ventilation requirement (and, in these cases, the maximal positive end expiratory pressure (PEEP) used), rescue therapies for refractory hypoxemia (alveolar recruitment and prone position ventilation), vasoactive drugs use, antiviral use (prescribed according to the Brazilian Ministry of Health guidance (initially treatment only of most severe cases with less than 48 hours evolution, and later broadened for all cases). The antiviral starting time according to symptoms onset was also evaluated;

5. Outcomes: mechanical ventilation free days over 28 days, ICU length of stay, ICU and in-hospital mortality.

Influenza A (H1N1) diagnosis was confirmed by specific polymerase chain reaction, initially performed by the Adolfo Lutz laboratory, belonging to the São Paulo State Health Secretary, and later by Laboratório Delboni (Diagnósticos da América S.A.), located in the study units. The test material used was oral and nasopharyngeal secretions.

### Statistical analysis

Categorical variables are shown as absolute numbers and ratios. The continuous variables are shown as medians and interquartile ranges (IQR). Patients requiring mechanical ventilation were compared to those who did not require. Categorical variables were compared using the chi-square test or Fisher's test, according to the ratios distribution. Continuous variables were compared using the Mann-Whitney test. Due to the small number of cases, a multivariate analysis was not conducted, to prevent data misinterpretation. The data analysis was conducted using the SPSS 10.0 version and Sigma Stat 2.03 software.

## RESULTS

Between July 1 and September 30, 2009, 22 patients were admitted to the two intensive care units, with later confirmed influenza A (H1N1)/2009 diagnoses. The median age was 30 (IQR 25-43.5) years, with female

predominance. Median time from symptoms-onset and hospital admission was 4 (IQR 2.25-6.5) days, and the most common symptoms were cough and fever. Comorbidities were common. Obesity, hypertension and asthma/COPD were the most common (Table 1). Two patients (9.1%) were pregnant, both in the third trimester. One of them underwent cesarean section in the ICU due to severe hypoxemic respiratory failure.

The reasons for the patients' ICU admission were acute respiratory failure (n=17; 77.3%) and severe sepsis (n=5; 22.7%). Both diagnoses were reported on the

**Table 1 –Patients demographic and clinical data**

Variable	Value
Age (years)	30 (25-43.5)
Female gender	14 (63.6)
SAPS 3	42 (37-49)
SOFA	2 (1-3.5)
Time from symptoms onset	4 (2.25-6.5)
Dyspnea	17 (77.3)
Cough	17 (77.3)
Fever	21 (95.5)
Myalgia	6 (27.3)
Diarrhea	4 (18.2)
Comorbidity*	11 (50.0)
Asthma/COPD	3 (13.6)
Hypertension	4 (18.2)
DM	2 (9.1)
Immunosuppression	3 (13.6)
Obesity	5 (22.7)
Pregnancy	2 (9.1)

SAPS - Simplified Acute Physiology Score; SOFA - Sequential Organ Failure Assessment; COPD - chronic obstructive pulmonary disease; DM - diabetes mellitus.

Results expressed as median (25%-75%) or number (%). \*The comorbidities total (n=19) is larger than the number of patients with any comorbidity (n=11) because some patients had more than one comorbidity.

ICU admission sheet. The overall patients' severity, as measured by the SAPS 3 and SOFA scores, was not high. Only 4 (18.2%) of the patients required vasopressor, and only 1 (4.5%) required dialysis support. The median ICU length of stay was 3 (IQR 1-5) days. ICU and in-hospital mortality was 4.5%. Oseltamivir was used for 17 (77.2%) patients, and in most (n=16; 94.1%) of them, was started within less than 48 hours from the symptoms onset.

Non-invasive mechanical ventilation was started in 4 (18.2%) patients, with a 50% failure rate. The failures were seen within less than 12 hours from the non-invasive ventilation onset. Patients without non-invasive ventilation failure were continuously under it for at least 24 hours, with equal or lower than 50% inspired oxygen fractions and lower than 10 cmH<sub>2</sub>O positive end expiratory pressure.

Invasive mechanical ventilation was required by 5 (22.7%) patients, and used for a median of 8.5 (IQR 3.25-10) days. The median mechanical ventilation-free days was 18 (IQR 8.5-23.5). High positive end expiratory pressures (PEEP) were used (median 16, IQR 10-25 cmH<sub>2</sub>O). Rescue therapy for refractory hypoxemia were used in two (40%) of the five patients who required mechanical ventilation, for one of them alveolar recruitment and for the other one prone position ventilation. Other patients admitted with respiratory failure (n=15) only required oxygen supplementation using a nebulizer or Ventury mask.

When patients who required invasive mechanical ventilation are compared with those who did not, no in-hospital mortality rate difference was found. Also no differences were found regarding age, comorbidities and body mass index. On the other hand, mechanical ventilation requiring patients were more severely ill, with higher SAPS and SOFA scores and lower starting PaO<sub>2</sub>/FiO<sub>2</sub> ratios (Table 2).

**Table 2 – Comparison between patients requiring or not mechanical ventilation**

	Invasive mechanical ventilation (N=5)	No invasive mechanical ventilation (N=17)	p value
Age	41.0 (24.5-55.5)	29.0 (25.0-38.0)	0.401
Female gender	5 (100)	9 (52.9)	0.115
SAPS 3	56 (46-74)	40.5 (37-42)	0.001
SOFA	7 (5-10)	2 (1-3)	<0.001
BMI	29.7 (23.6-34.7)	24.4 (22.7-32.5)	0.660
Comorbidities	3 (60.0)	8 (47.1)	0.99
Initial PaO <sub>2</sub> /FiO <sub>2</sub>	277.5 (199.2-389.5)	132.5 (40.2-199.2)	0.006
In-hospital mortality	1 (20)	0 (0)	0.185

SAPS - Simplified Acute Physiology Score; SOFA - Sequential Organ Failure Assessment; BMI - body mass index (calculated as the person's weight in kilograms divided by the square of his/her height expressed in square meters). Results expressed as median (25%-75%) or number (%).

Only one patient (4.5%) died. She was a 41 years old obese, hypertensive and diabetic patient. She was admitted five days after symptoms onset with acute respiratory failure. She was intubated at the emergency room and transferred to the ICU. The starting PaO<sub>2</sub>/FiO<sub>2</sub> ratio was 31, and the patient underwent alveolar recruitment using maximal 30 cmH<sub>2</sub>O PEEP. High dose noradrenalin was required, and the patient died 12 hours after ICU admission.

## DISCUSSION

Influenza A (H1N1)/2009 was the first XXI century pandemics. Large number of quickly disseminating cases was recorded, involving mainly young patients, as suggested by many published cohorts.<sup>(3,10,11,13-19)</sup> Given the large number of cases, although the disease's mortality was apparently low,<sup>(3,10,15-18)</sup> many patients were admitted to ICUs, leading to several studies reporting these cases clinical features and outcomes.<sup>(5-10,12,19-21)</sup>

In this study we revised data from 22 patients admitted to two private hospitals' intensive care units in São Paulo, Brazil. Our cohort has some data similarity with others, but part of our findings conflict with most of the literature reports.

Although these patients were young (median age 30 years), comorbidities were common. As with seasonal influenza infection, chronic diseases and immunosuppression are apparently risk factors for increased pandemic influenza infection severity.<sup>(9,10,15,16,18,19,22)</sup>

Obesity was described as one of the most important influenza A (H1N1)/2009 risk factors. In this study, 22.7% of the patients were obese, a 2 to 3 fold higher than the Brazilian population rate.<sup>(23)</sup> Overall, obese patients rate admitted to the ICU with complicated influenza A (H1N1)/2009 infections was higher than for the overall population in several studies.<sup>(9-12,15,19)</sup> The reason for increased morbidity in obese patients is not clear, but is likely to involve respiratory mechanics changes, coexistence with cardiovascular and metabolic diseases, or issues related to these patients treatment.<sup>(24)</sup>

In our cohort, the prevalence of pregnancy was 9.1%, and all of our pregnant patients were in their third trimester. Pregnancy, particularly during the third trimester, is a risk factor for respiratory complications and seasonal influenza admission.<sup>(22)</sup> This was reproduced in influenza A (H1N1)/2009 infection patients, where 2 to 12% of the cases were pregnant women.<sup>(6,7,14,15)</sup> Pregnancy was shown to be an isolated admission risk factor.<sup>(25)</sup> The severe infection risk was

7 times higher than for non-pregnant women, and when the gestational age was greater than 20 weeks, this risk raised to 13 times.<sup>(26)</sup>

According to data published, the main syndrome leading to patients' admission was acute respiratory failure. In our study, the ratio of patients requiring mechanical ventilation was low as compared with the literature.<sup>(5-11)</sup> This was probably due to less severely ill patients admitted to ICU in our cohort, as measured with the SAPS 3 and SOFA scores, which were the variables associated with invasive mechanical ventilation need. However, patients requiring mechanical ventilation remained on it for a prolonged time (median 8.5 days) and required high pressures, data similar to the literature reports.<sup>(5-12,19)</sup>

Interestingly, non-invasive ventilation failure occurred in one half of our patients. The failure rate was also high in other cohorts, 72% in a Mexican study,<sup>(8)</sup> 75% in Spain,<sup>(9)</sup> and 85% in Canada<sup>(7)</sup> and the United States.<sup>(12)</sup> This points to avoiding non-invasive ventilation in acute respiratory syndrome patients secondary to influenza A (H1N1)/2009 infection, or at least, do it carefully under strict monitoring.

Our cohort mortality rate was lower (4.5%) than in other studies, which ranged from 17 to 54%.<sup>(5-12)</sup> This finding can be explained by less severely ill patients in our cohort, whose SOFA score (median 2) was lower than in other cohort (mean 7 in the Spanish study;<sup>(9)</sup> 6,8 in the Canadian,<sup>(7)</sup> 9 in the Mexican,<sup>(8)</sup> 7 in the North-American<sup>(12)</sup>). This is probably because of more flexible admission criteria due to beds availability in Brazilian private institutions.

This study has obvious limitations. First, all patients were from private hospitals intensive care units in the city of São Paulo. Geo-economic aspects are likely to have impacted the results. Second, we describe data of only 22 patients, preventing any more detailed statistical analysis. Third, these patients were apparently less severely ill than those described in other cohorts. Therefore, we believe our data should be added to those generated from the initial pandemics experience.

## CONCLUSIONS

Our results highlight previous studies findings, suggesting that influenza A (H1N1) infection involved mainly young, especially obese, patients. In this cohort, patients were less severely ill than those described in previous cohorts, what explains the lower mortality and invasive mechanical ventilation requirement rates.

However, high positive end expiratory pressure needs were found in the patients who required invasive mechanical ventilation.

## RESUMO

**Objetivos:** Descrever a apresentação clínica e a evolução dos pacientes admitidos com diagnóstico de infecção por influenza pandêmica (H1N1) em duas unidades de terapia intensiva de hospitais privados de São Paulo.

**Métodos:** Foi realizada coorte retrospectiva com a avaliação de dados demográficos, da apresentação clínica inicial, escores prognósticos [*Simplified Acute Physiology Score* (SAPS) 3 e *Sequential Organ Failure Assessment* (SOFA)], comorbidades, de evolução e de tratamento de todos os pacientes que foram admitidos com diagnóstico confirmado de infecção por influenza pandêmico entre Julho e Setembro de 2009.

**Resultados:** Durante o período analisado, foram admitidos 22 pacientes. A mediana de idade foi de 30 (25-43,5) anos. As

medianas do SAPS 3 e do SOFA foram, respectivamente de 42 (37-49) e 2 (1-3,5). Comorbidades foram comuns (50%), especialmente a obesidade (22,7%). Duas (9,1%) pacientes eram gestantes. Cinco (22,7%) pacientes foram submetidos à ventilação mecânica, mas houve necessidade de altas pressões expiratórias nestes (mediana de 16cm H<sub>2</sub>O e intervalos interquartis 10-25cmH<sub>2</sub>O). A taxa de falha de ventilação não-invasiva foi de 50%. A maior parte (77,2%) dos pacientes foi tratada com oseltamivir. A mortalidade hospitalar foi de 4,5%. SAPS 3, SOFA e relação PaO<sub>2</sub>/FiO<sub>2</sub> iniciais associaram-se com a necessidade de ventilação mecânica (p<0,01).

**Conclusões:** A infecção por influenza pandêmico acometeu principalmente indivíduos jovens, especialmente obesos. Neste estudo, os pacientes eram menos graves que os descritos anteriormente, o que explica as menores mortalidade e necessidade de ventilação mecânica. No entanto, uma necessidade de altas pressões expiratórias nos pacientes que precisaram de ventilação mecânica.

**Descritores:** Vírus da influenza A subtipo H1N1; Surtos de doenças; Unidades de terapia intensiva; Respiração artificial

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