Severe virus influenza A H1N1 related pneumonia and community-acquired pneumonia: differences in the evolution

INTRODUCTION

Traditionally, viral pneumonia is considered less severe than bacterial community-acquired pneumonia (CAP). However, with the influenza A H1N1 (H1N1) outbreak in 2009, this assertion underwent a significant change because most of the infected individuals progressed to Acute Respiratory Distress Syndrome (ARDS) and, in many cases, death.\(^1\)

CAP is the leading cause of death from infectious diseases. The mortality rates are approximately 1% for outpatients and as high as 14% for hospitalized patients with severe CAP.\(^2\)

\(^1\) World Health Organization. Pandemic influenza A (H1N1) 2009: International update, 29 June 2009. Available from URL: http://www.who.int/csr/disease/swineflu/20090629/en/

\(^2\) Rello J, Mariscal M, Jimenez JR, Yuste J, Pacheco MM, Paya CH. Outcomes of patients with community-acquired pneumonia in a tertiary-care hospital. Am J Respir Crit Care Med 2000;161:1088-93.
The mortality rates among those who require hospitalization in intensive care units (ICU) are even higher for those who are admitted with CAP. The hospitalization rates in countries in the southern hemisphere ranged from 23.6 to 30.6% for individuals with influenza A H1N1 2009; among these, 11.7 to 18.5% (3.6 to 4.4% of the total number of cases) were admitted to ICUs. The mortality rates among those admitted to the ICU were 16% to 41%, and most of those patients required ventilatory support.

Considering the severely ill patients, there was a high incidence of ARDS, the most common cause of death. Its lethality seems to be similar to that of seasonal influenza, but it is greater than that reported for the respiratory coronavirus registered during the 2003 outbreak. A study conducted in 11 ICUs from six cities in the state of Paraná (Brazil) included 63 suspected and 37 confirmed H1N1 cases and reported that most of the patients were young and that the mortality rate was 39.7%.

The investigation of diagnostic and severity markers related to the nature of the infectious agent (bacterial versus viral) that caused the community-acquired pneumonia and those markers’ association with the clinical outcomes will allow that prediction of an unfavorable evolution, if present, and can guide earlier interventions and treatment. The present study aimed to determine the clinical, epidemiological and laboratory differences between critically ill individuals with community-acquired pneumonia and those with severe pneumonia caused by the influenza A H1N1 virus.

METHODS

Retrospectively and prospectively collected data from adult patients admitted to the Division of Critical Care (Mixed-24 bed ICU) of the Hospital de Base de São José do Rio Preto were analyzed. Data were collected between May 2009 and December 2010 from patients with a diagnosis of severe pneumonia caused by the influenza A virus H1N1 (H1N1). This study was approved by the Institutional Research Ethics Committee and informed consent was waived due to its observational nature.

The infection with influenza A H1N1 was diagnosed using the real time polymerase chain reaction (RT-PCR) of the nasopharyngeal secretion or respiratory tract specimens. Severe pneumonia caused by influenza A H1N1 was defined in the presence of fever >38°C, cough and clinical, laboratory and radiological conditions compatible with pneumonia and signs of worsening of the disease, which included the following: tachypnea (respiratory rate >25), hypoxia (arterial oxygen saturation \(\text{Sa}_2 \leq 92\% \) at room air and \(\text{Sa}_2 \leq 94\% \) in pregnant women), cyanosis, oliguria, altered level of consciousness, worsening of chronic disease and hypotension (systolic blood pressure <90 mmHg) or the use of vasopressor drugs (dopamine >5 \(\mu\)g/kg/minute or any dose of norepinephrine).

H1N1 patients were matched at a 2:1 ratio with cases of severe CAP admitted to the ICU. Thus, the data used for comparison came from consecutive patients who were admitted to the ICU with severe CAP during the same period and for whom the diagnosis of influenza A H1N1 had not been cogitated or the RT-PCR of nasopharyngeal or respiratory tract specimens were negative. Severe CAP requiring ICU admission was characterized by the presence of one major severity criteria (the need for mechanical ventilation or vasopressors) or two minor criteria (systolic blood pressure <90 mmHg or mean blood pressure <70 mmHg, arterial oxygen pressure/fractioin of inspired oxygen \([\text{PO}_2/\text{FiO}_2]\) <250, respiratory rate ≥30/minute, urea >19.6 mg/dL, altered mental status, multilobar pneumonia, platelets <100,000 cells/mm\(^3\), leukopenia - ≤4 x 10\(^9\) or hypothermia [body temperature ≤36°C]).

The laboratory data included in the analysis were obtained from the routine morning collection, which occurred between 5 and 6 am. Serum PCR levels were measured using turbidimetric immunoassay.

Statistical analysis

The results were expressed as the mean and standard deviation or median and 25\(^{th}\)-75\(^{th}\) percentiles. The statistical analysis used Student’s t test to compare two groups of normally distributed continuous variables, and the Mann-Whitney test was used for non-normal distributions. Descriptive statistics were calculated for the quantitative variables, and they were analyzed using Fisher’s test. P values <0.05 were considered significant.

RESULTS

The data of 45 patients were evaluated. Fifteen of those patients were admitted with H1N1 and 30 were admitted with CAP. The patients with H1N1 were younger (34.3±10.9 years versus 55.9±16.4 years in patients with CAP; p<0.001; Table 1). The proportion of patients requiring mechanical ventilation (86.7% versus 13.3%; p<0.05) and the mortality rate were higher in the H1N1 group than in the CAP group (53% versus 20%, respectively; p=0.056).
In patients with H1N1, the most frequent comorbidities were obesity, 53%; cardiovascular disease, 20%; and diabetes, 20%. In the CAP group, the most frequent comorbidities were cardiovascular diseases, 40%; tobacco smoking, 30%; and diabetes, 27% (Table 1). Obesity was significantly more prevalent in the H1N1 group (53%) than in the CAP group (6.6%), with p=0.02 (Table 1).

Compared with survivors, nonsurvivors of H1N1 were significantly older (40.2±9.2 versus 27.6±8.7 years; p=0.018), had higher serum lactate levels on admission (4.35±3.61 mEq/L; p=0.06) and had longer hospitalizations (not significant; Table 1).

Compared with patients from the control group, patients from the H1N1 group had significantly lower leukocyte counts (Day 1: 6,728±4,070 versus 16,038±7,863 and Day 2: 7,957±5,981 versus 14,130±6,514; p<0.05 for both) and significantly lower serum PCR levels (Day 2: 15.1±8.1 versus 22.1±10.9 mg/dL; p<0.05; Table 2). H1N1 nonsurvivors had significantly higher CRP levels compared with survivors (Day 1: 21.9±2.9 versus 6.9±4.8 mg/dL; Day 2: 20.5±3.5 versus 10.6±8.2 mg/dL; Day 3: 20.3±4.1 versus 8.1±9.3 mg/dL; Day 4, 16.1±5.5 versus 5.6±6.8 mg/dL; p<0.05 for all; Table 2).

The PaO$_2$/FiO$_2$ ratio was significantly lower during the first week for patients with H1N1 (Table 3). Nonsurvivors had lower PaO$_2$/FiO$_2$ values (Day 2: 54±43 versus 165±94) and higher plasma creatinine levels (Day 3: 1.72±0.59 versus 1.06±0.27 mg/dL; p<0.05) compared with survivors (Table 3). The platelet count values are described in table 3. Figure 1 shows the mean CRP (mg/dL) and PaO$_2$/FiO$_2$ for the H1N1 and CAP groups.

**DISCUSSION**

In the present study, we observed that, compared with patients who were admitted with bacterial CAP, the H1N1 group had younger patients and a higher prevalence of obesity. Significant differences were observed in the leukocyte count, CRP and oxygenation profiles, and higher mortality was observed in the H1N1 group.

Patients with diabetes mellitus, cancer, cardiovascular, respiratory and autoimmune diseases and pregnant women (especially those in the second and third trimesters of pregnancy) also showed increased susceptibility to more severe disease. In a Brazilian study, 27% of the patients with H1N1 were obese. Obesity has been reported as a risk factor for severity and mortality among patients with swine flu. A probable reason for this fact is the decrease in the functional residual capacity, which likely has an important impact during the evolution of H1N1.

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**Table 1 - Demographic data, clinical characteristics and outcomes from both groups**

|                  | H1N1 Total | H1N1 S | H1N1 NS | CAP Total | CAP S | CAP NS |
|------------------|------------|-------|--------|-----------|-------|-------|
| Number of patients | 15         | 7     | 8      | 30        | 24    | 6     |
| Male             | 9 (60.0)   | 6 (85.7) | 3 (33.3) | 21 (70.0) | 17 (70.8) | 4 (66.6) |
| Age (years)      | 34.3±10.9* | 27.6±8.7 | 40.2±9.2* | 55.9±16.4 | 58.2±18.9 | 55.3±16.1 |
| Lactate at admission (mEq/L) | 3.6±2.8 (N=7) | 1.53±0.85 (N=3) | 4.35±3.61 N= 4) | 3.1±1.9 (N=28) | 3.22±2.13 (N=22) | 2.7±0.98 (N=6) |

Comorbidities

|               | H1N1 Total | H1N1 S | H1N1 NS | CAP Total | CAP S | CAP NS |
|---------------|------------|-------|--------|-----------|-------|-------|
| Obesity       | 8 (53.3)*  | 3 (42.8) | 5 (62.5) | 2 (6.6) | 2 (8.3) | 0 (0.0) |
| CVD           | 3 (20.0)   | 1 (14.2) | 2 (25.0) | 12 (40.0) | 10 (41.6) | 2 (33.3) |
| Diabetes      | 3 (20.0)   | 2 (28.5) | 1 (12.5) | 8 (26.6) | 5 (20.8) | 3 (50.0) |
| Tobacco smoking | 2 (13.3)  | 0 (0.0) | 2 (25.0) | 9 (30.0) | 8 (33.3) | 1 (16.6) |
| COPD          | 1 (6.6)    | 0 (0.0) | 1 (12.5) | 6 (20.0) | 4 (16.6) | 2 (33.3) |
| Alcoholism    | 0 (0)      | 0 (0.0) | 0 (0.0) | 4 (13.3) | 3 (12.5) | 1 (16.6) |
| CRF           | 0 (0)      | 0 (0.0) | 0 (0.0) | 1 (3.3) | 1 (4.1) | 0 (0.0) |

Outcomes

|                | H1N1 Total | H1N1 S | H1N1 NS | CAP Total | CAP S | CAP NS |
|----------------|------------|-------|--------|-----------|-------|-------|
| Need for ventilator | 13 (86.7) | 7 (53.8) | 6 (43.2) | 3 (10.0) | 2 (66.6) | 1 (33.3) |
| Days of hospitalization | 8.0 (5.0-15.0) | 8.0 (6.0-11.0) | 8.5 (7.2-24.0) | 24 (15.7-28.2) | 27.0 (19.2-39.5) | 18.0 (9.0-3.7) |
| Days of ICU hospitalization | 4.0 (2.0-7.0) | 6.0 (4.0-7.0) | 10 (4.2-28.7) | 15.5 (8.7-4.2) | 18.0 (9.2-4.7) | 12.5 (7.2-8.2) |

CAP - community-acquired pneumonia; S - survivor; NS - nonsurvivor; CVD - cardiovascular disease; COPD - chronic obstructive pulmonary disease; CRF - chronic renal failure; ICU - intensive care unit. *p<0.05 versus CAP; #p<0.05 versus survivors. Results are expressed as number (%), mean±standard deviation (SD) or median (25%-75%).
Table 2 - Inflammatory parameters during the first week of hospitalization for the two groups, H1N1 and community-acquired pneumonia survivors and nonsurvivors

|          | H1N1 |          |          |          |          |          |  CAP  |          |          |          |          |          |
|----------|------|----------|----------|----------|----------|----------|-------|----------|----------|----------|----------|----------|
|          | Total | S        | NS       | Total    | S        | NS       |       |          |          |          |          |          |
| Leukocytes D1 | 6,728±4,070 (N=14) | 6,656±4,853 (N=7) | 6,600±3,511 (N=7) | 16,038±7,863 (N=29) | 16,587±8,157 (N=23) | 13,933±6,837 (N=6) |          |          |          |          |          |          |
| Leukocytes D2 | 7,957±5,981 (N=14) | 5,886±3,458 (N=7) | 10,029±7,453 (N=7) | 14,130±6,514 (N=27) | 15,376±6,841 (N=21) | 9,767±2,026 (N=6) |          |          |          |          |          |          |
| Leukocytes D3 | 9,867±6,674 (N=12) | 8,050±4,529 (N=6) | 11,683±6,869 (N=6) | 13,363±6,257 (N=29) | 13,410±6,270 (N=23) | 13,182±6,799 (N=6) |          |          |          |          |          |          |
| Leukocytes D4 | 9,565±5,962 (N=12) | 9,530±4,873 (N=6) | 96,00±3,739 (N=6) | 12,636±7,792 (N=28) | 13,070±8,513 (N=23) | 10,640±2,285 (N=5) |          |          |          |          |          |          |
| Leukocytes D5 | 10,691±5,657 (N=11) | 9,333±6,686 (N=6) | 11,600±4,375 (N=5) | 13,179±8,180 (N=28) | 13,665±8,826 (N=23) | 10,940±3,955 (N=5) |          |          |          |          |          |          |
| Leukocytes D6 | 11,210±5,821 (N=10) | 8,983±5,894 (N=6) | 14,550±4,355 (N=4) | 12,708±7,820 (N=13) | 13,291±8,375 (N=11) | 9,500±2,628 (N=2) |          |          |          |          |          |          |
| Leukocytes D7 | 10,919±4,460 (N=7) | 10,167±4,994 (N=3) | 11,483±4,707 (N=4) | 16,557±10,511 (N=7) | 15,800±8,004 (N=18) | 12,575±7,383 (N=4) |          |          |          |          |          |          |

CRP is an acute-phase protein released immediately after the start of the inflammatory or tissue injury process. CRP serum concentration is determined by its synthesis rate, which depends on the intensity of the inflammatory stimulus. Studies have demonstrated the utility of serial CRP measurements as a tool for the diagnosis and
monitoring of the response to CAP and nosocomial pneumonia treatment. A high CRP serum level on admission to the emergency room was a predictor of ICU admission and need for mechanical ventilation. However, the kinetics of serum CRP levels in patients with severe H1N1 pneumonia remain unknown to date.

Compared with patients from the CAP group, patients from the H1N1 group had significantly lower serum CRP levels and leukocyte counts, which suggest a lower inflammatory response compared with acute bacterial conditions and a possible viral infection. However, patients with H1N1 who did not survive had CRP levels that were higher than those of survivors and were similar to those found in the bacterial process. These data suggest that the patients who died had a stronger inflammatory response or a secondary bacterial infection.

A secondary bacterial infection was implicated in the increased morbidity and mortality of patients with influenza A H1N1 2009. The most commonly identified agents were Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae and gram-negative bacilli. In fatal cases of H1N1 virus infection, the most evident histopathological findings were different degrees of alveolar injury with the presence of hyaline membrane and septal edema, necrotizing tracheitis and bronchiolitis, pulmonary vascular congestion, alveolar hemorrhage, pulmonary thromboembolism and bacterial coinfection in 26 to 38%. A recent study reported that among patients with H1N1 infection, CRP serum levels were significantly higher in those who developed pneumonia compared with patients who did not develop pneumonia.

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\frac{\text{PaO}_2}{\text{FiO}_2}\ 
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values were significantly lower in patients with H1N1 than in patients with severe CAP who received mechanical ventilatory support. The main cause of death in patients with H1N1 is respiratory failure refractory to the usual mechanical ventilation. Currently, the use of extracorporeal membrane oxygenation in these patients seems to be one of the most effective measures for reducing mortality. The presence of severe hypoxemia in patients who died suggests that the medical centers that receive these patients should be prepared to offer this type of advanced life support to patients with severe hypoxemia.

The mortality rate in this series was 53% for patients with H1N1. Among ICU patients, the mortality rate is 16% to 41% in different series, and most of the patients required prolonged ventilatory support.

The major limitations of this study are its observational nature, the small sample size and the pairing performed by consecutive sample. Thus, other more adequate selection methods (such as the propensity score or by severity criteria) were not possible, which represent a potential selection bias). Other limitations were the inability to assess other markers of severity, such as procalcitonin and interleukin-6, and the fact that the study was conducted in a single center. However, the inclusion of a homogeneous population with severe forms of pneumonia supports the findings of the present study.

**CONCLUSION**

Usual laboratory tests may contribute to the differential diagnosis of severe community-acquired pneumonia and severe influenza A H1N1 pneumonia.

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RESUMO

Objetivo: Analisar dados clínicos, laboratoriais e de evolução de pacientes com pneumonia grave por vírus influenza A H1N1 em comparação à pneumonia bacteriana grave adquirida na comunidade.

Métodos: Estudo de coorte, retrospectivo. Todos os pacientes admitidos na unidade de terapia intensiva, entre maio de 2009 e dezembro de 2010, com diagnóstico de pneumonia grave por influenza A H1N1 foram incluídos. Trinta pacientes com pneumonia adquirida na comunidade grave admitidos no mesmo período foram usados como grupo controle. Pneumonia adquirida na comunidade grave foi definida como presença de ao menos um critério maior de gravidade (uso de ventilador ou vasopressor) ou de dois critérios menores.

Resultados: Foram avaliados os dados de 45 pacientes. Dentre eles, 15 pacientes com H1N1. Em comparação ao grupo com pneumonia adquirida na comunidade, pacientes do grupo H1N1 tiveram contagens de leucócitos significativamente menores na admissão (6.728±4.070 versus 16.058±7.863; p<0,05) e níveis de proteína C-reativa mais baixos (dia 2: 15,1±8,1 vs. 22,1±10,9 mg/dL, p<0,05). Os valores da relação PaO2/FiO2 foram menores na primeira semana em pacientes com H1N1. Não sobreviventes de pneumonia grave por H1N1 tiveram níveis significativamente mais elevados de proteína C-reativa do que os sobreviventes, além de níveis séricos mais altos de creatinina. A taxa de mortalidade foi significativamente mais elevada no grupo H1N1 do que no grupo controle (53% versus 20%, p=0,056, respectivamente).

Conclusão: Diferenças nos perfis de contagem de leucócitos, proteína C-reativa e de oxigenação podem auxiliar no diagnóstico e na avaliação do prognóstico de pacientes com pneumonia grave por vírus influenza A H1N1 e por pneumonia adquirida na comunidade.

Descritores: Pneumonia viral; Pneumonia bacteriana; Vírus da influenza A subtipo H1N1

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