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# Secondary infection and clinical aspects after pandemic swine-origin influenza a (H1N1) admission in an Iranian critical care unite

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## ABSTRACT

**Objective:** A new flu virus (H1N1) swine origin and cause of human infection with acute lung disease was published in the world and led to many patients were admitted in intensive care unit (ICU).

**Materials and Methods:** In a prospective descriptive study, all ICU patients in a pulmonary disease specialist hospital between April 2010 and July 2011 with confirmed infection (H1N1) were evaluated. Information including demographic, clinical and microbiology using Statistical Package for Social Sciences (SPSS) software version 16 was studied and classified.

**Results:** Of 46 patients hospitalized with confirmed diagnosis of swine flu pneumonia (H1N1), 20 cases (43.7%) admitted in ICU out of which 10 cases were males (50%), the mean age was 36.9 and the range was 21-66 years. Nine patients (45%) had underlying diseases. Most underlying disease was respiratory disease in which four cases (20%) were of asthma and one patient had chronic obstructive pulmonary disease (COPD). No admission of pregnant patient with swine flu was reported in the ICU. Cough and sputum were the most frequent symptoms (19 patients equal 95%). Four patients (20%) were admitted with decreased level of consciousness and five cases (25%) died during hospitalization.

**Conclusion:** It seems, swine flu with high mortality and transfer rates is a worldwide health problem. Because of limited treatment regimen, the risk of secondary infection and high need to intensive care in H1N1 pneumonia, environmental control, including vaccination of high risk people and public announcement, make determining role in controlling of this disease.

**Key Words:** Intensive care unit, swine flu, secondary infection

## INTRODUCTION

New influenza A virus (H1N1) originated from swine caused human infections, that is, acute pulmonary disease during the spring of 2009 in Mexico[1,2] and after primary disease expansion in the United States and Canada,[3,4] the virus was disseminated worldwide. By March 2010, almost all countries had reported some cases of the disease and more than 17,700 deaths among patients with definite laboratory diagnosis of H1N1 were reported to the World Health Organization (WHO).[5]

Total cases with definitive laboratory diagnosis significantly indicated were lower than the rate of predicted pandemic. In the United States, about 59 million cases, 265,000 hospitalizations, and 12,000 deaths due to H1N1 occurred up to mid of February 2010.[6]

Underlying conditions that related to seasonal flu complication are the same risk factors for H1N1 in 2009. Pregnancy, the 2nd week after delivery, and patients with a suppressed immune system or neurological disease were risk factors of disease.[7-9]

Also among the sever or fatal cases of H1N1, severe obesity (body mass index ≥35), five to 10 times against general population have been reported.[7,9,10]

H1N1 infection caused a wide range of clinical syndromes, upper respiratory tract involvement without fever up to severe viral pneumonia. Mild illness without fever in 8-32% of those infected has been reported.[11]

Most patients referred for treatment had symptoms like typical influenza illness as fever and cough symptoms that sometimes was associated with sore throat and was rhinorrhea.[2,8,11-14] The major clinical syndrome leading to hospitalization and intensive care unit (ICU) was viral pneumonia with sever hypoxia, acute respiratory distress syndrome (ARDS), sometimes systemic shock, and renal failure.[9,10] Rapid progress is common, typically on the 4$^{th}$ or 5$^{th}$ day, that incubation during the first 24 h after admission is necessary.

Radiological findings including mixed and disseminated interstitial infiltration and alveolar infiltration, although multilobar and lobar involvement, especially in patients with bacterial coinfection of the lower lobe is seen.[8] According to different health system's involvement in the epidemic H1N1 and the importance of flu cases were hospitalized in ICU mortality, this study reviewed the admitted cases of confirmed H1N1 pneumonia in the ICU at our center.

## MATERIALS AND METHODS

A prospective study of patients with confirmed H1N1 pneumonia who were admitted in ICU of Masih Daneshvari Hospital, a referral hospital in Tehran, Iran, due to disease severity from April 2010 until end of February 2011.

Blood samples of patients were examined with real-time reverse-transcription polymerase chain reaction (RT-PCR) and patient's throat discharge swab was cultured and evaluated with RT-PCR. Clinical, laboratory, and demographic data were collected as questionnaires. Demographic information including age, sex, smoking, alcohol consumption history, drugs abuse, and disease symptoms before mechanical ventilation was collected and if they were unconsciousness, the data was asked from their family. Clinical and radiographic data, microbiological results of blood, and secretion samples during hospitalization in ICU patients were collected using medical records.

Statistical analysis using Statistical Package for Social Sciences (SPSS) version 16 was performed. Comparing binary variables (bivariate value), Chi-square, and Fisher's exact test for continuous variables such as age, weight, duration of hospitalization, the first with Kolmogorov-Smirnov test was investigated for continuances, and then Student's *t*-test or Chi-square was performed. *P* less than 0.05 ($P < 0.05$) was considered as a significant difference.

## RESULTS

Of 46 patients hospitalized with confirmed swine flu (H1N1) pneumonia, 20 cases (43.7%) that were required to hospitalize in the ICU were studied. From these cases, 10 cases were males (50%), the average age was 36.9 years with the lowest being 21 years old and the maximum was 66 years old. None of these patients had history of alcohol consumption, but four cases (20%) were active smokers and seven cases (35%) had history of oral or inhalation opium consumption. Two patients (10%) had experience of drug injection in the recent 3 months.

In the study of clinical symptoms, 19 patients (95%) were noted to have cough, sputum 19 (95%), dyspnea 18 (90%), chest pain 11 (55%), and body pain or myalgia 14 (70%). None of the patients had complained of sore throat. Four patients (20%) had loss of consciousness. Clinical symptoms are given in Table 1.

In the next stage, underlying diseases were investigated. Comorbidity was seen in nine patients (45.9%). Diabetes, history of steroid use, valvular heart disease (VHD), autoimmune diseases, organ transplant, and pregnancy history was not observed in any of patients.

Chronic renal failure (CRF) in one patient (5%), one case of infection with human immunodeficiency virus (HIV; 5%), one case of hypertension (HTN; 5%), and one case of malignancy (5%) was observed. Four cases with history of asthma (20%) and one patient (5%) with chronic obstructive pulmonary disease (COPD) was included.

In laboratory studies; aspartate aminotransferase (AST); alanine aminotransferase (ALT); lactate

**Table 1: Clinical symptoms of hospitalized patients with confirmed H1N1 in ICU**

| Variable | No. (%) |
|---|---|
| Cough | 19 (95) |
| Hemoptysis | 11 (55) |
| Sputum | 19 (95) |
| Dyspnea | 18 (90) |
| Pleuritic chest pain | 11 (55) |
| Myalgia | 14 (70) |
| Fever | 18 (90) |
| Chilling | 10 (50) |
| Sweating | 10 (50) |
| Headache | 1 (5) |
| Abdominal pain | 1 (5) |
| Diarrhea | 7 (35) |
| Vomiting | 4 (20) |
| Loss of consciousness | 4 (20) |
| Total | 20 |

ICU: Intensive care unit

dehydrogenase (LDH); creatine phosphokinase (CPK); and serum electrolytes such as K, Na, and Ca; and erythrocyte sedimentation rate (ESR) were examined. The average values (mean) and standard deviations are given in Table 2.

The levels above normal for CPK enzymes in 13 cases (65%), LDH in 17 cases (85%), AST in 13 cases (65%), and ALT in eight cases (40%) was observed. Serum electrolytes examination in three patients showed hyponatremia (15%) with serum sodium level below 135 mEq/ml and hypernaremia was not observed. Only one patient (5%), had hypokalemia with potassium 1.16 mEq/ml. In nine patients (45%), serum creatinine was higher than 1.1 mg/dl.

Also five patients (25%) had leukocytosis (white blood cell (WBC) greater than 10,000) and four patients (20%) had leukopenia at time of admission. Thrombocytopenia (platelets less than 100,000) in 11 cases (55%) was observed. Seven patients (35%) had anemia.

Three patients had positive blood cultures: One case (5%) *Pseudomonas aeruginosa*, one case *Escherichia coli*, and one case of Acinetobacter spp was seen. Culture of sputum or endotracheal tube aspiration was positive for six patients, two of which (10% of all patients and 33.3% of culture positive cases) were positive for *Pseudomonas aeruginosa* and four (20% of all patients and 7.66% of positive cultures) for Acinetobacter. Overall sputum and blood cultures included three cases of *Pseudomonas aeruginosa* (15%), five cases of Acinetobacter spp (25%), and one case of *E. coli* (5%) [Table 3].

**Table 2: Laboratory data of hospitalized patients with confirmed H1N1 in ICU**

| Mean ± SD | Variable |
|---|---|
| 638.6 ± 696.1 | CPK |
| 1144.9 ± 727.6 | LDH |
| 151.3 ± 193.3 | AST |
| 110.3 ± 199.6 | ALT |
| 136.0 ± 4.0 | Na |
| 4.1 ± 1.1 | K |
| 1.4 ± 1.6 | Cr |
| 47.5 ± 36.4 | ESR |
| 6.4 ± 3.5 | CRP |

ICU: Intensive care unit, CPK: Creatine phosphokinase, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, CRP:C-reactive protein

**Table 3: Microbiological finding in hospitalized patients with confirmed H1N1 in ICU**

| Variable | No. (%) | | |
|---|---|---|---|
| | Pseudomonas | Acinetobacter | *Escherichia coli* |
| Positive blood culture | 1 (5) | 1 (5) | 1 (5) |
| Positive trance bronchial washing | 2 (10) | 4 (20) | - |
| Total | 3 (15) | 5 (25) | 1 (5) |

ICU: Intensive care unit

Eight patients (40%) took mechanical ventilation. The mean of Acute Physiology and Chronic Health Evaluation (APACHE) score was more than 20 for all patients and oseltamivir was administered. Also, broad spectrum antibiotics were started including ceftriaxone, azithromycin and vancomycin. Nineteen patients (95%) received intravenous corticosteroid concurrently. Only for two patients (10%) intravenous immunoglobulin (IVIG) was administered.

Hospital outcome of these patients before discharge was partial recovery in 15 cases (75%) (which were discharged and outpatient follow-up was done) and five patients (25%) expired in hospital.

Radiologic examination included four cases (20%) of consolidation, six cases of infiltration (30%) as more patchy infiltration, and 10 cases (50%) ground glass opacity view. Four patients (20%) had associated pleural effusions. In two cases (10%), pneumothorax was observed that did not require a chest tube. Radiological lesions in two cases (10%) were unilateral and in 18 cases (90%) were bilateral.

## DISCUSSION

As it is obvious, in this study, the possibilities of molecular investigation such as PCR to identify other types of viral pneumonia and drug resistance is not available and bacterial defining has been done by conventional methods. Ribonucleic acid (RNA) virus detection using traditional methods or RT-PCR is the best for early detection of 2009 H1N1 virus.[15] Nasopharyngeal aspiration with swab immediately after onset of illness symptoms would be appropriate example; but endobronchial aspiration, in patients with lower respiratory tract disease have a higher value.[15-17]

In the recent study, the number of men and women was equal, which may be an incidental finding. Another study in Canada by Kumar *et al*.,; out of 215 patients, 162 confirmed, six probable, and 47 suspected to H1N1 and 113 patients (67.3%) were female. In the study conducted in Australia and New Zealand including 856 patients who were admitted to the ICU, 376 patients (52.1%) were women out of which 66 patients (9.1%) were pregnant. In our study, no case of pregnancy was found. In recent reviews, age below 20 years was not observed, and the majority of patients (75 percent) were aged 20-40 years. In other studies, most hospitalized cases were children less than 5 years, especially less than 1 year[18] and in adults less than 65 years.[7] H1N1 pandemic in the United States was presented by 32-45% with age less than 18 years old. So, the statistics are different. Since, our center is not a pediatric hospital, our result is expected.

Mostly patients presented with nonspecific lower respiratory infection clinical features such as cough, dyspnea, sputum, fever, chest pain, myalgia, chills, abdominal pain, and diarrhea. The gastrointestinal symptoms are higher than seasonal flu,[19,20] with seven cases (35%) of diarrhea and abdominal pain. In the current study, sore throat was not seen and it could be an incidental finding.

In the study of underlying diseases, immune system suppression and neurological disease are risk factors for catching H1N1.[7,8] On the other hand, specific physiological conditions such as pregnancy and BMI over 35, are risk factor in increasing incidence and mortality.[7,9,10] On the other hand, it is possible that cardiovascular and lung disease such as COPD are involved in complications. In a study in Australia and New Zealand, 32.7% cases of asthma or COPD was observed. About diseases that are suspected to suppress the immune system, that is, autoimmune diseases, diabetes, and history of steroid use; no items were found in this study. In contrast, a case of HIV infection and one case of CRF was observed.

Basic laboratory findings are typical normal leukocyte or lymphopenia.[10-21] In the current study, almost normal and abnormal leukocyte was equal and same number of cases of leukocytosis (five cases equal 25%) and leukopenia (4 cases equal 20%) were seen. High levels of CPK and LDH has been associated with worse prognosis. In the recent study, patients in most cases have been associated with increased enzyme levels including 65% increase in CPK, 85% increase in LDH, and 65% increase in AST levels. Almost all fatal cases had increased LDH and CPK.

The most common radiologic finding was ground glass opacities (GGO). In other studies, the results showed mixed and scattered infiltration or alveolar infiltration.[8] In cases of possible empyema, brief pleural effusion was observed.

In the study by Rizzi *et al*., in Italy, 40 patients were studied, 15 (37%) had interstitial changes, five cases had GGO only (12%), three cases had GGO and consolidation, and in nine cases GGO and interstitial changes was observed. In our study, 11 patients (30%) were unilateral and 28 cases (70%) had bilateral changes and it seems that mostly bilateral GGO appearance has been seen. In our study, four cases (10%) with pleural effusion were also observed.[22]

In various studies conducted in 2009 about bacterial pneumonia in these patients, especially patients admitted in ICU and those who have died; the most commonly observed were *Staphylococcus aureus*, which is usually resistant to methicillin, and *Streptococcus pneumoniae*. In our study, the most confirmed germ was Acinetobacter spp. which indicated nosocomial infection.

On the other hand, most of these patients were referred from other centers, often have received broad spectrum antibiotics; the rate of *Streptococcus pneumoniae* was low in their blood and tracheal aspiration culture. Treatment results in a quarter caused death and the rate varies in different studies, but in any case indicates that the mortality rate is high.[7,8,23-27]

During the review, a number of patients required hospitalization in ICU, out of which 25% patients died. It seems, swine flu with high mortality rate and transmission is a worldwide health problem and there is limited treatment and because of secondary infection in these patients, environmental control including public notice, individual hygiene, and vaccination of high risk people has decisive role in preventing this disease instead of treating patients.

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## REFERENCES

1. Echevarria. Zuno S, Mejia-Arangure JM, Mar-Obeso AJ, Grajales-Muñiz C, Robles-Pérez E, González-León M, *et al.* Infection and death from influenza A H1N1 virus in Mexico: A retrospective analysis. Lancet 2009;374:2072-9.
2. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, *et al.* Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009;361:680-9.
3. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, *et al.* Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360:2605-15.
4. Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, *et al.* Antigenic and genetic characteristics of swine-origin 2009 A (H1N1) influenza viruses circulating in humans. Science 2009;325:197-201.
5. Pandemic (H1N1) 2009 - update 94. Geneva: World Health Organization, April 1, 2010. Available from: www.who.int/csr/don/2010_04_01/en/index.html [Last accessed 2010 Apr 9].
6. CDC estimates of 2009 H1N1 influenza cases, hospitalizations and deaths in the United States, April 2009–February 13, 2010. Atlanta: Centers for Disease Control and Prevention, 2010. Available from: http://flu.gov/individualfamily/about/h1n1/estimates_2009_h1n1.html [Last accessed 2010 Apr 9].
7. Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, *et al.* Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. JAMA 2009;302:1896-902.
8. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, *et al.* Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med 2009;361:1935-44.
9. The ANZIC Influenza Investigators, Webb SA, Pettilä V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, *et al.* Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009;361:1925-34.
10. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, *et al.* Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA 2009;302:1872-9.
11. Libster R, Bugna J, Coviello S, Hijano DR, Dunaiewsky M, Reynoso N, *et al.* Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 2010;362:45-5.

12. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, *et al*. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009;361:2507-17.
13. Estadisticas: Influenza A (H1N1). Mexico City: Secretaria de Salud, May 29, 2009. Avaialable from: http://portal.salud.gob.mx/contenidos/noticias/influenza/estadisticas.html [Last accessed 2010 Apr 9].
14. Hackett S, Hill L, Patel J, Ratnaraja N, Ifeyinwa A, Farooqi M, *et al*. Clinical characteristics of paediatric H1N1 admissions in Birmingham, UK. Lancet 2009;374:605.
15. Clinical management of human infection with pandemic (H1N1) 2009: Revised guidance. Geneva: World Health Organization, November 2009. Available from: http://www.who.int/csr/resources/publications/swineflu/clinical_ management/en/index.html [Last accessed 2010 Apr 9].
16. Fleury H, Burrel S, Balick Weber C, Hadrien R, Blanco P, Cazanave C, *et al*. Prolonged shedding of influenza A (H1N1) v virus: Two case reports from France 2009. Euro Surveill 2009;14.
17. Blyth CC, Iredell JR, Dwyer DE. Rapid-test sensitivity for novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;361:2493.
18. Transmission dynamics and impact of pandemic influenza A (H1N1) 2009 virus. Wkly Epidemiol Rec 2009;84:481-4.
19. Witkop CT, Duffy MR, Macias EA, Gibbons TF, Escobar JD, Burwell KN, *et al*. Novel influenza A (H1N1) outbreak at the U.S. Air Force Academy: Epidemiology and viral shedding duration. Am J Prev Med 2010;38:121-6.
20. Human infection with new influenza A (H1N1) virus: Clinical observations from Mexico and other affected countries, May 2009. Wkly Epidemiol Rec 2009;84:185-9.
21. Dominguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, *et al*. Critically Ill patients with 2009 influenza A (H1N1) in Mexico. JAMA 2009;302:1880-7.
22. Lisena EF, Schininà V, Lauria F, Ferraro F, Bibbolino C, Rovighi L, *et al*. Radiological findings of pneumonia in patients with swine-origin influenza A virus (H1N1). Radiol Med 2010;115:507-15.
23. Presanis AM, De Angelis D. New York City Swine Flu Investigation Team. Hagy A, Reed C, Riley S, Cooper BS, *et al*. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: A Bayesian analysis. PLoS Med 2009;6:e1000207.
24. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: A cross-sectional serological study. Lancet. 2010 Mar 27;375:1100-8.
25. Donaldson LJ, Rutter PD, Ellis BM, Greaves FE, Mytton OT, Pebody RG, *et al*. Mortality from pandemic A/H1N12009 influenza in England: Public health surveillance study. BMJ 2009;339:b5213.
26. Tabarsi P, Moradi A, Marjani M, Baghaei P, Hashemian SM, Nadji SA, *et al*. Factors associated with death or intensive care unit admission due to pandemic 2009 influenza A (H1N1) infection. Ann Thorac Med 2011;6:91-5.
27. Pereira JM, Moreno RP, Matos R, Rhodes A, Martin-Loeches I, Cecconi M, *et al*. ESICM H1N1 Registry Steering Committee, ESICM H1N1 Registry Contributors. Severity assessment tools in ICU patients with 2009 Influenza (H1N1) pneumonia. Clin Microbiol Infect 2012;18:1040-8.


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