Severe Pneumonia Associated with Pandemic (H1N1) 2009 Outbreak, San Luis Potosí, Mexico

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We describe the clinical characteristics and outcomes of adults hospitalized with pneumonia during the pandemic (H1N1) 2009 outbreak. Patients admitted to a general hospital in San Luis Potosí, Mexico, from April 10 through May 11, 2009, suspected to have influenza virus–associated pneumonia were evaluated. We identified 50 patients with suspected influenza pneumonia; the presence of influenza virus was confirmed in 18: 11 with pandemic (H1N1) 2009 virus, 5 with unsubtypeable influenza A virus, 1 with seasonal influenza A virus (H3N2), and 1 in whom assay results for seasonal and pandemic (H1N1) viruses were positive. Eighteen patients were treated in the intensive care unit, and 10 died. During the pandemic (H1N1) 2009 outbreak, severe pneumonia developed in young adults who had no identifiable risk factors; early diagnosis and treatment of influenza virus infections may have a determinant role in outcome.

A novel influenza A virus, pandemic (H1N1) 2009 virus, has been identified as the cause of an epidemic outbreak of respiratory illness throughout the world (1). Current information indicates that the pandemic (H1N1) 2009 virus has been circulating in Mexico since at least March 2009 and that it has been the cause of an increase in the number of hospitalizations of young adults since April 2009 (1). The city of San Luis Potosí played a major role in raising awareness of the presence of an unusual and nonsubtypeable influenza A virus during the early days of the outbreak (2).

The Hospital Central “Dr. Ignacio Morones Prieto” is a public hospital located in San Luis Potosí that served as a reference center for evaluation and treatment of patients with suspected influenza virus pneumonia. In this article, we describe the results of investigations performed to determine the etiology of this outbreak and report the clinical findings, treatments, and patient outcomes.

Patients and Methods

Study Site

The city of San Luis Potosí is located in central Mexico and is the capital of the state of San Luis Potosí (3). The state population was 2,410,414 in 2005; the population of the San Luis Potosí metropolitan area in the same year was 957,753 (4). The Hospital Central provides medical services to mid- and low-income populations from all areas of the state; it has 269 beds in total, 250 in adult and pediatric wards and 19 in the intensive care unit (ICU).

Patients

Starting April 10, 2009, when the first case of pandemic (H1N1) 2009 was identified, all patients admitted to Hospital Central with lower respiratory tract infections (LRTIs) were screened for the presence of influenza virus. Patients who experienced acute onset of respiratory symp-
Clinical, Laboratory, and Bacteriologic Information

Patients admitted to medical wards and the ICU were subjected to the hospital’s standard diagnostic protocol: blood cultures, HIV antibody testing, chest radiograph, laboratory tests, and spontaneous or induced sputum samples for Gram staining and culture. These tests were performed at admission and every 48–72 hours thereafter. Patients receiving mechanical ventilation had samples for minibrachioalveolar lavage (mini-BAL) (5), blood, and urine sent for bacterial cultures at admission and every 48–72 hours, or in the event of new or persistent fever. Bronchoscopy with BAL was performed as clinically indicated. A quantitative threshold of 10^5 CFU/mL for mini-BAL was used and of 10^4 CFU/mL for BAL (6). Patients were treated with at least the following standard antimicrobial drug regimens: those with criteria for acute lung injury (ALI; partial pressure of oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] = 201–300) or acute respiratory distress syndrome (ARDS, PaO_2/FiO_2<200) received ceftriaxone and/or vancomycin plus levofloxacin or clarithromycin, and patients treated in medical wards received levofloxacin. Therapeutic decisions were individualized by the attending physician. Deceased patients for whom the family granted consent were subjected to postmortem examinations to recover lung specimens for bacteriologic culture, influenza virus detection, and histopathologic analysis.

Sample Collection and Processing

Respiratory samples obtained from patients with suspected influenza infection were placed in either normal saline or viral transport media and kept refrigerated at 4°C until their arrival at the laboratory. A 200-μL aliquot of these samples was used for RNA extraction, and the remaining volume was stored at −70°C. Viral RNA was isolated using the High Pure Viral RNA Kit (Roche Diagnostics, Mannheim, Germany). Sample collection and processing were carried out according to national and international biosafety guidelines and recommendations (7,8).

Influenza Virus Detection

A multiplex reverse transcription–PCR (RT-PCR) capable of distinguishing type A from type B influenza virus was developed based on previously published primers (9). One-step RT-PCR was performed using the Access RT-PCR System (Promega Corporation, Madison, WI, USA) at 48°C for 45 min, followed by 94°C for 2 min, 40 cycles of 30 s at 94°C, 30 s at 56°C, 30 s at 72°C, and a final step at 72°C for 5 min. Influenza A samples were subsequently subtyped using a multiplex PCR with sequence specific primers approach adapted from previous publications (Table 1) (/1). PCR products were subjected to electrophoresis on 1.5% agarose gels prestained with ethidium bromide at 6 volts/cm for 45 min and digitally documented. An RT-PCR for detection of pandemic (H1N1) 2009 virus was developed based on early sequencing data (EpiFlu Database, http://platform.gisaid.org). RT was carried out at 38°C for 45 min by using UniFlu-RT oligonucleotide; PCR involved the newly developed Sw-NS-F 5′-ATG-GAC-TCC-AAC-ACC-3′ and Sw-NS-R 5′-TTA-AAAT-AAG-CTG-AAA-CGA-G-3′ oligonucleotides at 1.6 μmol/L final concentration, 0.02 IU/μL of Taq (Vivantis Technologies Sdn Bhd Selangor D.E., Malaysia), 200 μmol/L deoxynucleoside triphosphates, and 1.5 mmol/L MgCl_2. PCR program was 95°C for 5 min, followed by 15 cycles of 95°C for 20 s, 54°C for 30 s, and 72°C for 1.5 min, and a final step of 2 min at 72°C. One microliter of a 1:1 dilution of the first PCR product was then used in a second PCR by using similar components except 1 mmol/L MgCl_2 and 800 mmol/L final concentration of internal oligonucleotides Sw1-F 5′-CTT-
GAA-AGA-GGA-ATC-GAG-CG-3' and Sw1-R 5'-GTC-TCC-CAT-TCT-CAT-CAC-AGT-3' (429-bp amplicon). Influenza virus detection at the Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE) and the State Public Health Laboratory used the real-time RT-PCR protocol developed by the US Centers for Disease Control and Prevention (CDC).

**Virologic and Epidemiologic Data**

To assess the presence of respiratory syncytial virus (RSV) and influenza in the community we reviewed the database at the Virology Laboratory Universidad Autónoma de San Luis Potosí (UASLP) and recorded the weekly number of viral detections from January 2008 through May 2009. In addition, the weekly number of acute respiratory infections (ARI) reported in the state of San Luis Potosí and the emergency department (ED) at the Hospital Central was recorded.

**Statistical Analysis**

We analyzed demographic and clinical characteristics using descriptive statistics. Means or medians were used for description of continuous variables according to data distribution; categorical variables were described with the use of percentages. Comparisons among patient groups were made to assess factors associated with severe infections. We compared categorical variables using the chi-square or Fisher exact test; continuous variables were compared by using the Student t test or Mann-Whitney U test, according to data distribution. A p value <0.05 was considered significant. Statistical analyses were performed with SPSS for Windows (version 14.0, SPSS Inc., Chicago, IL, USA).

**Results**

An ARI outbreak was recorded in San Luis Potosí during April and May 2009. The most characteristic feature observed at the beginning of this outbreak was an increase in severe pneumonia cases requiring hospitalization of young adult patients. The Figure shows the epidemiologic curve of the weekly number of ARI cases reported to Servicios de Salud en el Estado de San Luis Potosí (state public health services) from January 2008 through May 2009 and the weekly number of ARI-related consultations provided in the ED at Hospital Central. In addition, the percentage of samples that were positive for influenza and RSV during each week at the Virology Laboratory UASLP is presented.

Pneumonia patients included in this report were admitted during epidemiologic weeks 14 through 18 at a time that maximal pandemic (H1N1) 2009 virus circulation was documented.

From April 10 through May 11, 2009, a total of 70 patients >18 years of age were admitted to the Hospital Central with suspected LRTI. After review of clinical, radiologic, and laboratory data, suspected influenza virus–related pneumonia was diagnosed for 50 of those patients; other patients were determined to have cholangitis and ARDS (1 patient), congestive heart failure (2 patients), aspiration pneumonia (2 patients), asthma without evidence of pneumonia on chest radiograph (5 patients), and influenza-like syndrome without pneumonia (10 patients). Nine of the 20 excluded patients were tested for influenza infection, and results were negative for 8; samples from 1 of the patients found to have influenza-like illness without radiographic evidence of pneumonia were positive for pandemic (H1N1) 2009 virus.

The main demographic features of our group of 50 patients are summarized in Table 2. Only 1 patient had an underlying pulmonary disorder. Obesity was the most frequent underlying disorder and was the only underlying disorder in 17 patients; 6 patients had morbid obesity (body mass index [BMI] >40). The most frequent symptoms patients had at hospital admission were fever (100%), headache (96%), cough (94%), and myalgias (94%). The predominant radiologic pattern on chest radiograph was consolidation, with multilobar and unilobar consolidation in 39 and 11 patients, respectively. Twenty-one patients had ill-defined interstitial opacities. Three patients had evidence of unilateral pleural effusion that affected ≥10% of the hemithorax. HIV testing was performed for 45 patients; all results were negative. Evidence of a systemic inflammatory response and muscle involvement was observed commonly, manifested by el-

![Figure](image-url)
evated levels of C-reactive protein, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST).

Thirty patients were treated in medical wards, 12 of whom met criteria for ALI, none had extrapulmonary involvement, and all were discharged to home. Two patients with ARDS were treated in the ER.

Eighteen patients were treated in the ICU (17 with ARDS and 1 with ALI). The median positive end expiratory pressure at admission was 16 cm H2O (range 14–20 cm). The median positive end expiratory pressure with ARDS were treated in the ER.

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**Research**

**Table 2. Demographic features of 50 adult patients admitted with acute pneumonia during the pandemic (H1N1) 2009 outbreak, San Luis Potosí, Mexico**

| Characteristic                      | Value                               |
|------------------------------------|-------------------------------------|
| Age, y, mean (SD, range)           | 38.4 (13.9, 21–69)                  |
| Gender                             |                                     |
| M                                  | 29 (58)                             |
| F                                  | 21 (42)                             |
| Residence                          |                                     |
| San Luis Potosi municipality       | 30 (60)                             |
| Other municipality                 | 20 (40)                             |
| No. home contacts, median (range)  | 4 (1–16)                            |
| Presence of ≥1 underlying condition| 30 (60)                             |
| Obesity (BMI > 30)                 | 25 (55.6)†                          |
| Diabetes mellitus                  | 8 (16)                              |
| Other conditions‡                  | 9 (18)                              |
| Smoker                             | 13 (26)                             |
| Arrival at the hospital            |                                     |
| Directly                            | 40 (80)                             |
| Referred from other hospital or clinic | 10 (20)                          |
| Influenza vaccination during previous winter season | 5 (10) |

*Values are no. (%) unless otherwise indicated. BMI, body mass index. †BMI data available only for 45 patients. ‡Some patients had >1 additional underlying condition, including chronic renal failure (3), underlying heart disorder (3), systemic lupus erythematosus (1), chronic obstructive lung disease (1), hyperthyroidism (1), seizure disorder (1), and pregnancy (1).

The duration of symptoms at the time of sample collection for samples that tested positive for influenza virus at the start of antiviral drug treatment ranged between 1 and 14 days (median 6 days). Four patients that did not receive antiviral drugs were discharged. The only patient who did not receive antiviral drugs and died was the first patient with pandemic (H1N1) 2009–associated pneumonia to be admitted to our hospital during this outbreak; he had severe pneumonia and ARDS and died in the ED.

All patients were treated with antimicrobial drugs. Levofloxacin or clarithromycin was included as part of the antimicrobial drug treatment of 48 (96%) patients; the 2 patients who did not receive 1 of these antimicrobial drugs recovered and were discharged to home. Sixteen patients received steroids as part of their treatment; steroid use was assessed by the attending physician. The median number of days from admission to start of steroid treatment was 2 days (range 0–20 days). The effect of steroid use on patient outcome is difficult to assess because this treatment was used more frequently in patients with more severe disease.

Postmortem open lung biopsies were performed on 5 patients and a complete necropsy was performed for 1. The pathologic findings were those of diffuse alveolar damage; additionally, some patients had hemophagocytosis and capillary and arteriolar thrombosis as well as enlargement of alveolar cells. One patient had acute bacterial pneumonia.

Respiratory samples from 45 patients were available for viral detection. Samples from 37 patients were tested at UASLP, while samples from 41 patients were tested at InDRE in Mexico City or the State Public Health Laboratory in San Luis Potosí using the real time RT-PCR protocol developed by CDC. Overall, influenza virus was detected in respiratory secretions of 15 (33.3%) of the 45 patients who had respiratory samples available for testing; pandemic (H1N1) 2009 virus was detected for 10 patients, seasonal influenza A virus was detected for 4, and results of assays for pandemic (H1N1) 2009 and seasonal influenza A viruses were positive for 1 patient. Subtyping of samples positive for seasonal influenza virus showed that 1 infection was caused by influenza A (H1N1) virus (this finding corresponded to the patient with positive results for both seasonal and pandemic [H1N1] 2009 virus; due to the potential for cross-reactivity, infection with pandemic [H1N1] 2009 virus only cannot be ruled out in this patient) and 1 by influenza A (H3N2); the other 3 samples were not subtypeable by our RT-PCR. In addition, RT-PCR was performed in lung tissue from 6 patients who died; the presence of influenza virus was detected in 3 of these patients (pandemic [H1N1] 2009 virus in 1 and unsubtypeable influenza virus in 2). Detection of influenza virus in respiratory samples from these deceased patients was either negative (in 2 patients) or not possible because no respiratory sample was collected before the patient’s death (1 patient).

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UASLP was significantly shorter (mean of 4.7 days) compared with those samples that tested negative (8.8 days; \( p = 0.02 \)). Duration of symptoms at the time of sample collection was also demonstrated to be statistically significant for samples that tested positive with the use of CDC’s real time RT-PCR protocol (mean 5.7 days) compared with those that were negative by this method (mean 9.5 days; \( p = 0.006 \)).

We compared the demographic and clinical characteristics of patients with pandemic (H1N1) 2009 infections and those that were negative on viral testing (Table 3). The clinical presentation of both groups of patients was similar.

Sputum cultures obtained at time of admission were positive in 4 patients treated in medical wards; bacteria isolated included *Staphylococcus aureus* (2 patients) and...

| Characteristic                                      | Pandemic (H1N1) 2009 (n = 11) | Nonconfirmed influenza (n = 32) | \( p \) value |
|----------------------------------------------------|-------------------------------|---------------------------------|---------------|
| Demographic features                               |                               |                                 |               |
| Male sex                                           | 5 (45.5)                      | 20 (62.5)                       | 0.48          |
| Age, y, mean (SD)                                  | 34 (10.97)                    | 39.47 (14)                      | 0.25          |
| Resident of San Luis Potosi municipality            | 5 (45.5)                      | 20 (62.5)                       | 0.73          |
| Clinical features                                  |                               |                                 |               |
| Presence of underlying conditions                  |                               |                                 |               |
| Obesity (BMI >30)†‡                                  | 4 (40)                        | 16 (57.1)                       | 0.47          |
| Diabetes                                           | 2 (18.2)                      | 4 (12.5)                        | 0.64          |
| Other conditions‡                                    | 3 (27.3)                      | 4 (12.5)                        | 0.35          |
| Days from symptom onset to admission, mean (SD)    | 5.36 (2.5)                    | 6.72 (3.13)                     | 0.2           |
| Duration of symptoms at the onset of dyspnea, d, mean (SD) | 2.73 (1.19) | 3.91 (1.92)                     | 0.06          |
| Pneumonia severity index (PORT score)              | 2.82 (1.47)                   | 2.81 (1.15)                     | 0.99          |
| Symptoms                                           |                               |                                 |               |
| Fever                                              | 11 (100)                      | 32 (100.0)                      | NA            |
| Headache                                           | 10 (90.9)                     | 31 (96.9)                       | 0.45          |
| Cough                                              | 11 (100)                      | 31 (96.9)                       | 1             |
| Myalgias                                           | 9 (81.8)                      | 32 (100.0)                      | 0.06          |
| Arthralgias                                        | 10 (90.9)                     | 30 (93.8)                       | 0.06          |
| Dyspnea                                            | 11 (100)                      | 25 (78.1)                       | 0.16          |
| Rhinorrea                                          | 8 (72.7)                      | 25 (78.1)                       | 0.69          |
| Malaise                                            | 6 (54.5)                      | 11 (34.4)                       | 0.29          |
| Blood-streaked sputum                              | 3 (27.3)                      | 13 (40.6)                       | 0.49          |
| Diarrhea                                           | 1 (9.1)                       | 7 (21.9)                        | 0.66          |
| Pleuritic chest pain                               | 1 (9.1)                       | 5 (15.6)                        | 1             |
| Vomiting                                           | 2 (18.2)                      | 2 (6.3)                         | 0.27          |
| Physical examination findings on admission          |                               |                                 |               |
| BMI, mean (SD)                                     | 29.17 (6.48)                  | 31.22 (5.4)                     | 0.34          |
| Respiratory rate, bpm, mean (SD)                   | 28.44 (4.91)                  | 28.31 (7.24)                    | 0.92          |
| Crackles                                           | 0.03                          |                                 |               |
| Unilateral                                         | 4 (36.4)                      | 2 (6.3)                         |               |
| Bilateral                                          | 7 (63.6)                      | 30 (93.8)                       |               |
| Wheezing                                           | 5 (45.5)                      | 18 (56.3)                       | 0.73          |
| Laboratory features                                |                               |                                 |               |
| Total leukocyte count on admission (x 10^{9}/L), median (SD) | 8.81 (6.1) | 6.81 (4.13)                     | 0.23          |
| Platelet count (x 10^{9}/L), mean (SD)§            | 173.6 (61.48)                 | 227 (216.24)                    | 0.45          |
| C-reactive protein, mg/dL, mean (SD)                | 14.51 (8.45)                  | 18.74 (16.22)                   | 0.41          |
| Creatinine, mg/dL, median (SD)                      | 1.24 (0.87)                   | 1.11 (0.75)                     | 0.13          |
| Creatine phosphokinase, U/L, mean (SD)             | 376.78 (439.22)               | 462.2 (507.27)                  | 0.65          |
| Lactate dehydrogenase, U/L, median (SD)§           | 952 (674.72)                  | 1089.31 (602.32)                | 0.54          |
| AST, mg/dL, median (range)¶                         | 43 (19–76)                    | 69 (18–249)                     | 0.07          |
| ALT, mg/dL, median (range)#                        | 29 (13–55)                    | 43 (13–177)                     | 0.05          |

*Values are no. (%) unless otherwise indicated. BMI, body mass index; bpm, breaths per minute; PORT, Pneumonia Patient Outcomes Research Team (www.ahrq.gov/clinic/pneuclin.htm); NA, not available; AST, aspartate aminotransferase; ALT, alanine transaminase.‡Data available for 38 patients.

†Includes chronic renal failure, systemic lupus erythematosus, pregnancy, cardiac disorder, seizure disorder.

§Data available for 42 patients.

¶Data available for 41 patients.

#Data available for 40 patients.
Pneumonia is recognized as the most important complication of influenza infections (13). LRTI in patients with influenza may be caused directly by viral invasion or result from bacterial complications (14,15). The occurrence of progressive disease, with bilateral pulmonary consolidation or ARDS, associated with high death rates has been described for patients with influenza-associated pneumonia, particularly in those with infections caused by new subtypes of influenza virus. In contrast, bacterial pneumonia complicating influenza usually occurs after near resolution of influenza symptoms (16,17). Our study cohort was composed mostly of young adults without severe cardiovascular or pulmonary underlying disorders in whom the onset of dyspnea was, on average, 3.5 days after the onset of influenza symptoms. In only 4 (8%) of the 50 patients included in this report was there clear evidence of the participation of bacteria in the disease process; this number contrasts with previous reports of community-acquired pneumonia, for which bacteria are reported more frequently. Our results suggest that bacterial co-infection played a minor role as a cause of pneumonia in these patients. In addition, no histopathologic evidence of bacterial pneumonia was observed in 5 of the 6 deceased patients on whom lung biopsies were performed.

Although we were not able to confirm pandemic (H1N1) 2009 virus in all patients, several factors support the notion that a high proportion of their infections were caused by this virus. These factors include the clustering of cases of severe pneumonia in young adults (>85% of the patients became ill during a 2-week period) coincident with the identification of a novel influenza virus shown to be circulating in the community.

A striking feature observed in this cohort of patients was the high frequency of systemic involvement with laboratory evidence of myositis/rhabdomyolysis, elevated acute-phase reactants, ARDS, hemodynamic instability, and acute renal failure. Elevation of LDH levels has been reported for patients with seasonal influenza but has not been considered a specific marker of severity. Elevation of CPK levels was frequently observed in patients treated at our hospital, and elevation of CPK and AST levels suggest that muscle inflammation was present in these patients. Myositis (with or without rhabdomyolysis) has been associated previously to influenza infections (18–21). Of note, elevated CPK levels were observed in patients with and without confirmed influenza virus infections.

Why these severe manifestations of influenza infections occurred in young adult patients during this outbreak remains an unanswered question. Although almost two thirds of patients hospitalized with pneumonia at our institution had underlying health disorders, the presence of chronic respiratory or cardiovascular diseases were rare. Obesity was the most frequent underlying disorder and was present in
more than half of the patients; in contrast, the prevalence of obesity for adults >20 years of age in San Luis Potosí was 31.3% in 2006 (22). Eight of 10 patients who died were obese, including 4 who were morbidly obese. Obesity has been suggested to be a proinflammatory chronic condition and thus may have contributed to some of the manifestations observed in these patients (23,24). The presence of obesity as a possible risk factor for severe pandemic (H1N1) 2009 has been noted previously. In a report from Michigan, 9 of 10 patients with pandemic (H1N1) 2009 infection requiring intensive care were obese (25). However, larger studies are needed to determine the role of obesity as a risk factor for severe influenza pneumonia.

There are several limitations to our study. First, only pneumonia patients were included. Therefore, the effect of obesity as a cause of hospitalizations is probably underestimated because patients with exacerbations of chronic obstructive pulmonary disease and asthma, as well as with congestive heart failure decompensation triggered by influenza, may have been excluded. Second, we did not have appropriate respiratory samples from all patients admitted with pneumonia because some patients were admitted before the existence of an outbreak had been identified. In addition, patients with more severe infections tended to have a longer duration of illness at the time of admission, reducing the likelihood that influenza may have been detected. Third, influenza infection could not be confirmed in most patients, and other causes of acute pneumonia (such as other viruses) were not excluded. However, because the clinical manifestations were similar in all cases, patients became ill in a short period simultaneously with a sudden increase in ARI in San Luis Potosí, and pandemic (H1N1) 2009 infections were detected at a time when RSV and seasonal influenza circulation had declined, we consider it is likely that many cases may have been caused by influenza virus.

During the pandemic (H1N1) 2009 outbreak in San Luis Potosí, Mexico, young adults without identifiable risk factors became ill with severe pneumonia. Until predictors of severe pandemic (H1N1) 2009 virus infections are identified, early diagnosis and prompt antiviral treatment seem to be the best measures to avoid serious illness caused by this virus (26,27).

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