Clinical Study

Clinical Findings in Albanian Patients with 2009 Influenza AH1N1 Admitted at the Intensive Care Unit

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Due to the ease of cross-continent spread of infectious diseases, the 2009 influenza AH1N1 (H1N1) affected many countries. This observational prospective study looked at Albanian patients admitted with 2009 H1N1 at the ICU of the Department of Infectious Diseases at the University Hospital Center of Tirana, from November 2009 to March 2010. Demographic data, symptoms, comorbidities, and clinical outcomes were collected from each patient. The number of days spent in the ICU was recorded for each patient along with their radiological and laboratory findings, and outcome at discharge. Critical illness occurred in 31 patients admitted with confirmed 2009 H1N1. The median age of patients was 35 years. Five (16.1%) patients required endotracheal intubation; noninvasive oxygen therapy (NIV) was used in 15 (48.4%) patients via nasal tube; and continuous positive airway pressure (CPAP) and pressure support ventilation (PSV) oxygen masks were used in 11 (35.5%) patients. All patients were treated with oseltamivir. Four patients admitted and treated did not survive. Critical illness in the setting of 2009 H1N1 admitted in the ICU predominantly affected young adults. NIV could play a role in treating 2009 influenza H1N1 infection-related hypoxemic respiratory failure that was associated with severe hypoxemia, pneumonia, requirement for prolonged mechanical ventilation, and the frequent use of antiviral therapy.

1. Introduction

In April 2009, a new strain of human H1N1 influenza A virus (H1N1) was identified in the US [1, 2]. The number of H1N1-related cases worldwide showing symptoms ranging from fever and cough to diarrhea and vomiting was in the thousands [3, 4]. Along with the aforementioned symptoms, the influenza H1N1 virus has been associated with acute respiratory distress syndrome and pneumonia [5, 6].

The first laboratory-confirmed case of novel pandemic influenza H1N1 2009 in Albania was reported on May 2009. From July to October 2009, Albania experienced a moderate

wave of viral transmission; a stronger wave began in November, and a peak in H1N1 incidence occurred during the first week of December 2009. The hospitalization rates were reported every week during the influenza season, which allowed for the collection of information on the number of people with influenza-related complications and total number of such patients admitted into the ICU (Figure 1). The aim of this study was to describe clinical characteristics of ICU admissions, demographic characteristics, and compare treatments to their respective outcomes among critically ill patients with laboratory-confirmed H1N1 virus. Treatment methods include the use of antiviral, and if

necessary, antibacterial agents. A matter of debate is which administration mode for the ventilatory support system (oxygen therapy) is more effective. This treatment can be deemed necessary because of the risk of severe lung infection as a result of the H1N1 infection.

2. Methods

The Albanian Ethical Committee approved this observational prospective study. The case-series described the clinical and epidemiologic characteristics of 31 patients with laboratory-confirmed influenza H1N1 infection admitted to the ICU of

TABLE 1: Characteristics of the 31 study patients who had confirmed infection with 2009 influenza H1N1 virus.

Variable	<i>N</i>	%
Gender		
Male	13	42
Female	18	58
Age group (total)		
0–5 yr		
6–10 yr		
11–15 yr	1	3.2
15–50 yr	22	71.0
>50 yr	8	25.8
Age group (deceased)		
0–5 yr		
6–10 yr		
11–15 yr		
15–50 yr	2/22	9.1
>50 yr	2/8	25.0
Symptoms/outcome		
Fever (temperature > 38°C)	31	100.0
Myalgia or arthralgia	28	90.3
Headache	25	80.6
Acute respiratory distress	12	38.7
Productive cough	30	96.8
Chronic illnesses	11	35.5
Endotracheal intubation	5	16.1
Death	4	12.9
Days from onset of symptoms to admission—median (range)	4	(2–7)
Days from admission to death—median (range)	3.5	(1–6)
Laboratory findings—median (range)		
Leukocyte count—per mm ³	6800	1670–20,000
Lymphocyte count—per mm ³	1690	770–4800

the Service of Infectious Diseases at the University Hospital Center, Tirana, Albania, during the period November 15, 2009–March 27, 2010. Data were collected and analyzed regarding (1) influenza-like illness (ILI) visits to the emergency department; (2) ILI hospitalizations; (3) confirmed 2009 H1N1 admissions. In all cases, days of stay at the ICU, X-ray thoracic examinations and CT examinations, laboratory serologic findings, and metabolic panels were examined. Blood gases were measured. Each patient's outcome at discharge was also documented. Nasopharyngeal-swab specimens were collected at admission, and bronchial-aspirate samples were obtained after tracheal intubation. Specimens were tested by RT-PCR at the National Influenza Laboratory (Institute of Public Health), in accordance with the WHO protocol [7]. All study patients had confirmed influenza H1N1 2009 infection.

FIGURE 3: Bilateral patchy alveolar opacities in X-ray examination. (a) A patient at hospitalization (b) a patient after 3 days of treatment.

TABLE 2: Comparison between the patients that died and survived amongst the 31 study patients with confirmed influenza H1N1 virus.

Variable	Patients who survived (N = 27)	Patients who died (N = 4)	Hazard ratio for death (95% CI)	P value
Age				
Median	32	50	1	0.5
Range	15–78	19–55	0.96–1.07	
Gender				
Female number/total number	15/27	3/4	1.8 (0.2–17.4)	0.6
Days from illness onset to admission				0.5
Median	4	4.5	1.2	
Range	2–7	4–6	0.6–2.4	
Lymphocyte count per mm ³				0.48
Median	1850	1465	0.96	
Range	770–4800	890–3020	0.9–1.1	
Endotracheal intubation	1/27	4/4		0.01**
PaO ₂ (mm Hg)				0.21
Median	70.4	60.8	0.94	
Range	43.1–90	54.9–63.5	(0.9–1.0)	
PaCO ₂ (mm Hg)				0.16
Median	33.7	41.0	1.18	
Range	22.8–44.8	31.5–41.5	(0.9–1.4)	
Oximetry O ₂ -Sat				0.07
Median	87	64	0.91	
Range	57–93	64–79	(0.8–1.0)	
pH				0.02
Median	7.4	7.3	6.01×10^{-13}	
Range	7.3–7.5	7.32–7.43	0.0–0.013	
PaO ₂ /FiO ₂ (mm Hg)				0.03
Median	171	61	0.92	
Range	86–250	52–101	0.84–0.98	
Acute resp. distress syndrome	9/27	3/4	4.8 (0.51–46.0)	0.1
BE				0.07
Median	–1.3	–3.7	0.6	
Range	–6.5–8	–4.5––2.1	0.4–1.1	
Opacity in three or four lung quadrants in initial radiograph—no./total no.	14/27	3/4	2.5 (0.26–23.8)	0.4

**Logrank test.

TABLE 3: Frequency of underlying conditions in hospitalized patients infected with H1N1 influenza virus and survival outcome.

Comorbidity/Condition	Survived <i>n</i> (%)	Deceased <i>n</i> (%)
Pregnancy		2 (50)
Arterial hypertension	3 (11.1)	
Arterial hypertension and Diabetes		1 (25)
Chronic respiratory disease	2 (7.4)	
Obesity	2 (7.4)	
Cardiac insufficiency or valvulopathy		1 (25)
Renal transplant	1 (3.7)	
Congenital heart disorder	1 (3.7)	
Psychiatric disorders	1 (3.7)	

2.1. Statistical Analysis. Data analysis was conducted using SPSS Statistical Software 18. Days of stay in the ICU and patient outcome at discharge were recorded for each patient. Clinical characteristics were compared between patients who died and those who survived. Cox proportional-hazards regression was used to analyze the effect of several risk factors on survival. The comparison of survival curves for patients requiring endotracheal intubation in the first 24 hours after admission was done using the log-rank test. All reported *P* values are two-sided and were not adjusted for multiple testing.

3. Results

3.1. Patients' Data. Characteristics of the 31 study patients with confirmed 2009 influenza H1N1 infection are listed in Table 1. The ages of the patients ranged from 15 to 78 years (median age: 35 years). Twenty-two patients (71%) were between 15 and 50 years of age, and eight of them (25.8%) were over 50 years of age.

The time between onset of symptoms and admission to the hospital ranged from two to seven days (median, four days), and hospitalization lasted between four days and four weeks (Table 2, Figure 2). All patients had fever with temperatures higher than 38°C, cough with sputum, and dyspnea or respiratory distress. Four (12.9%) patients had emesis and nine (29%) had abdominal pain. None of the patients had diarrhea.

3.2. Underlying Condition. Twelve patients (38.7%) had pre-existing medical conditions, and two patients were pregnant. Four patients had arterial hypertension, one patient had diabetes mellitus and hypertension, two patients had chronic respiratory disease, two patients were obese, one patient suffered from congenital heart disorder, one suffered from psychiatric disorders, and one patient previously had a renal transplant. Two of the deceased patients were pregnant, one of the deceased patients had both hypertension and diabetes, and one deceased patient had mitral stenosis (Table 3). None of the patients had undergone seasonal influenza vaccination

in 2008-2009, and none of them had a history of pneumococcal vaccination. None of the patients sought medical care at other institutions as outpatients before hospitalization and were not treated with antibiotics.

3.3. Laboratory Findings. Twenty-six patients (83.9%) had pneumonia confirmed with radiological examination. This examination revealed bilateral patchy alveolar opacities (predominantly basal) affecting three or four lung quadrants in 17 patients (Figure 3, Table 2). Findings on chest radiographs were consistent with the acute respiratory distress syndrome in all patients requiring mechanical ventilation.

3.4. Clinical Course during Hospital Stay and ICU Monitoring. Respiratory distress requiring endotracheal intubation developed in five patients within the first 24 hours after admission. Of the five patients that required endotracheal intubation, the four patients that passed away had a median oxygen saturation of 64% in the absence of supplementary oxygen. Noninvasive oxygen therapy (NIV) was used in 15 patients (48.4%) via nasal tube. Continuous positive airway pressure (CPAP) and pressure support ventilation (PSV) oxygen masks were used in 11 patients (35.5%). Altered consciousness was found in nine (29%) patients. The respiratory tract was free of inflammatory obstructions or foreign bodies.

Regarding hemodynamic parameters, arterial hypotension was the predominant symptom. Only four patients presented with arterial pressure values over 150 mmHg. With respect to pulse oximetry, SpO₂ ranged from 57 to 93%, while diuresis was generally maintained at a median of 2l/24 h (range 200–2700 mL).

3.5. Treatment. Treatment protocol was followed based on the recommendation of the Centers for Disease Control and Prevention [5]. None of the patients had been treated with oseltamivir before admission; all patients received it in the hospital at a dose of 75 mg twice a day for a minimum of five days. After admission, 19 patients received ceftriaxone and six received clarithromycin. Additional antibiotics were prescribed to several patients on the basis of their clinical course. Additional therapy consisted of the administration of prednisolone (50–100 mg/24 h), oxygen therapy, enteral nutrition, parenteral liquids and electrolytes, vitamins, human albumin, and comorbidity-related medications.

Of the 31 patients, five patients required endotracheal intubation. Four out of the five patients requiring endotracheal intubation died. Overall, out of the 31 patients, 27 patients recovered and were discharged from the hospital. Patients died between one and six days (median, 3.5 days) after admission (Table 1).

4. Discussion

The 2009 influenza H1N1 epidemics rapidly spread around the world due to increased travel and communication between countries [8]. The pathology (mostly shown in previously healthy patients) had an influenza-like symptomatology that progressed during a period of four to seven days.

Pneumonia and other findings developed during the first day of hospital admission generally fulfilled the criteria of acute lung injury or acute respiratory distress syndrome (ARDS) [9–11]. The development of acute lung injury or ARDS was shown in our patients.

The occurrence of this symptom can lead to patient death. A contributing factor for lethal outcome in our patients may have been due to a delay in seeking medical care and the subsequent delayed admission to a hospital. Albania has also reported a large number of persons with mild disease, through the national surveillance system for influenza with 545 reported cases of AH1N1 infection confirmed from May 2009 to March 2010 (among more than 3000 suspected subjects); of them, 363 were admitted to the University Hospital Center of Tirana [12, 13]. The 31 patients in this study showed relatively severe altered conscience and ventilation, compared to other subjects. Among our patients, four out of five patients (80%) requiring endotracheal intubation did not survive, and the lung damage was most likely due to the primary effect of infection with influenza virus. Other authors have reported similar results [14–16].

In our study, 12 subjects had comorbidities and two patients were pregnant. There was no difference between benign and fatal outcome patients in the association with comorbidities. A history of lung disease, obesity, diabetes, hypertension, psychiatric, and heart disease were the most common comorbidities in our study. Comorbidity presence was a risk factor for severe or atypical disease pattern [12]. Another study reported similar comorbidity rates (36%) with regards to 2009 H1N1 patients in Chile [17]. The relative absence of serious comorbidities in our sample emphasizes that young, relatively healthy adults were the primary population affected by severe 2009 influenza H1N1 infection during this outbreak.

Ventilatory support indication was based upon evaluation of clinical condition of the patients and measurement of arterial blood gases. According to our data, 61% of patients required ventilator support for profound hypoxemic respiratory failure, requiring high levels of inspired oxygen and positive end expiratory pressure (PEEP). The survival rate was higher in NIV than in patients with endotracheal intubation. NIV application rapidly improved vital signs and oxygenation and relieved the patients from tachypnea. Similarly to some reports, none of the patients who received oxygen therapy via nasal sound/mask and NIV required invasive ventilation [18, 19]. Also, evaluation of the fluid status was performed regularly to avoid hypovolemia (hemodynamic instability).

Several studies have shown that noninvasive ventilatory support may decrease mortality obviating the need for endotracheal intubation [16, 19]. In general, patients respond to NIV within 24 hours. Nonresponders who will eventually need endotracheal intubation can thus be identified early. Our findings are consistent with these reports, pointing out that NIV is effective and safe in the context of 2009 influenza H1N1 infection. The complex therapy that includes non-invasive oxygen-support was an effective tool in the management of patients with pandemic influenza H1N1. Moreover, the early administration of oxygen yielded excellent results

in the prevention of respiratory complications from the pandemic H1N1 influenza [20, 21]. Our experience with this technique provides strong evidence that NIV can play a role in treating acute respiratory failure patients, reducing the need of ICU beds and improving outcomes.

This is the first study that reported about systematic monitoring of influenza admission at the ICU in Albania. A limitation of this study is the relatively small sample size, and the patient population consists of patients from a single center. Thus, the use of multivariate analysis was not attempted for patients with fatal outcome.

NIV is recommended for patients with H1N1 virus infection complicated by pneumonia, acute lung injury, and ARDS because it improves oxygenation and reduces the work of breathing in these patients, but treatment should also be based upon published, evidence-based guidelines for sepsis-associated ARDS. In fact, standard lung-protective ventilation strategies are appropriate initially [22, 23].

5. Conclusion

It could be concluded that pandemic H1N1 influenza is associated with severe hypoxemic respiratory failure, often requiring prolonged mechanical ventilation. The reason for the severe hypoxemia observed in these patients and the mode of oxygen therapy application is still of debate. However, NIV could be used based on the results in 2009 influenza H1N1 infection-related hypoxemic respiratory failure by decreasing atelectatic alveoli, improving pulmonary compliance, and reducing work of breathing. Early diagnosis by the consistent symptoms of fever and a respiratory illness during times of outbreak, with prompt treatment of neuraminidase inhibitors and aggressive support of oxygenation failure and subsequent organ dysfunction, may provide better opportunities to mitigate the progression of illness and mortality observed during this severe pathology.

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