A retrospective evaluation of critically ill patients infected with H1N1 influenza A virus in Bursa, Turkey, during the 2009–2010 pandemic

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Abstract

Background: H1N1 influenza A virus infections were first reported in April 2009 and spread rapidly, resulting in mortality worldwide. The aim of this study was to evaluate patients with H1N1 infection treated in the intensive care unit (ICU) in Bursa, Turkey.

Methods: Demographic characteristics, clinical features, and outcome relating to H1N1 infection were retrospectively analysed in patients treated in the ICU.

Results: Twenty-three cases of H1N1 infection were treated in the ICU. The mean age of patients was 37 years range: (17–82). Fifteen patients were female (65.2%). The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 19 range: (5–39). The most common symptoms were dyspnea (73.9%), fever (69.6%), and cough (60.9%). Mechanical ventilation was required for all patients. Oseltamivir and antibiotics were administered to all patients. Six (26.1%) patients died. APACHE II scores were higher in the deceased 28.5 range: [16–39] vs. 14 range: [5–28] in survivors; $p = 0.013$).

Conclusion: When compared to the literature, the demographic, epidemiological, and clinical characteristics were similar in the cases we encountered. The mortality rate was high despite the use of appropriate treatment. We believe that the high mortality is related to higher APACHE II scores. The H1N1 virus should be considered in community acquired pneumonia, especially in younger patients presenting with severe pneumonia.

Key words: pandemic influenza, H1N1 infection, critically ill patient, intensive care unit

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Introduction

In 2009, millions of people worldwide were affected by the rapid person-to-person spread of the H1N1 influenza A virus[1,2]. In June 2009, the World Health Organisation (WHO) declared a level 6 warning for this new influenza pandemic[3].

The H1N1 virus spread aggressively in Turkey during October 2009–January 2010, reaching a peak during weeks 46–47 of 2009[4]. During the second half of 2009, influenza cases were seen in to the city of Bursa. The first patient was admitted to the pulmonology department of Uludag University Hospital on the 12th of November 2009, and then admitted to our ICU on the 15th of November 2009 as the first critically ill patient with respiratory failure due to H1N1 infection. Uludag University Hospital is the only tertiary care centre established by the government in Bursa, and is also the major reference centre for the southern Marmara region. Bursa is the fourth largest city in Turkey, with a population of approximately 2 million residents.

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As the first pandemic of the 21st century, this infection primarily affected those with underlying respiratory and cardiac disease, children, young adults, and pregnant women[2,5,6]. Although early symptoms similar to seasonal influenza were observed, cases of H1N1 infection progressed to viral pneumonia, respiratory failure, hypoxia, and organ failure resulting in death[6-8]. Some cases were treated in the ICU, and mortality was reported to be 5%–50%[7-12].

This retrospective study describes the demographic characteristics, clinical features, and outcome of adult patients with severe H1N1 virus infection who were treated in the ICU for respiratory failure from November 2009 to February 2010.

Methods

The study was approved by the Hospital Ethics Committee. A retrospective analysis of patients diagnosed with H1N1 influenza A infection who were treated in the ICU of Uludag University Hospital in Bursa, Turkey, during November 2009 to February 2010 was carried out.

Features of the ICU and the hospital

The ICU of Uludag University Hospital's Anesthesiology Department is a 19-bed mixed (surgical and medical) unit that cares exclusively for adult patients. There are a total of 6 doctors (3 senior consultants and 3 anaesthesiology residents) caring for the patients. Additionally, a senior consultant from the Infectious Diseases Department examines the patients on a daily basis. Admission to the unit is based on many indications, including acute respiratory failure requiring invasive/non-invasive mechanical ventilation, which is relevant to this study.

Patients and assessment

Data related to the epidemiology of the cases and the treatment process were considered. A record was made of age, gender, presence of co-morbidity, pregnancy or childbirth within the previous 28 days, initial symptoms, and time from reporting of the initial symptoms to admittance to the ICU and evaluation of APACHE II scores. Individuals with a body mass index (BMI) of 30–40 were classified as obese, whereas those with a BMI >40 were considered as morbidly obese.

An examination was made of the pulmonary radiographic findings collected during each patient's ICU stay; PaO2/FiO2 ratios, laboratory parameters (leucocytes, thrombocytes, urea, creatinine, aspartate aminotransaminase, alanine aminotransaminase), treatments applied during hospitalisation (invasive mechanical ventilation [IMV], non-invasive mechanical ventilation [NIMV], antiviral therapy, antibiotherapy and corticosteroids), virological validation results, duration of ICU stay, and mortality were evaluated.

Statistical analysis

Statistical analysis was carried out using SPSS 13.0 (Statistical Package for Social Sciences). The conformity of the variables to normal distribution was examined using the Shapiro–Wilk test. Continuous and discrete variables were expressed as median values (minimum-maximum). The Mann-Whitney U, Pearson Chi-Square, and Fisher exact chi-square tests were used in the comparison of variables between groups. Categorical variables were expressed numerically and as percentages. The risk factors affecting mortality were analysed with logistic regression analysis. A value of $p < 0.05$ was accepted as statistically significant.

Results

During the study period, 23 patients with a diagnosis of H1N1 infection were treated in the ICU. All patients who were suspected to have contracted H1N1 were admitted to the ICU based on the WHO case definitions[13]. A respiratory sample was obtained for virological validation from all patients, and polymerase chain reaction testing was performed.

The mean age of the patients was 37 years (17–82 years). Fifteen patients were female (65.2%) and 8 were male (34.8%). There were 4 pregnant women and 1 postpartum patient. The 4 pregnant women gave birth by Caesarean section during the treatment period. Twelve (52.2%) patients were admitted directly to the ICU from the emergency room, 6 (26.1%) from the hospital clinics, and 5 (21.7%) were transferred from surrounding hospitals. The demographic characteristics and co-morbidities of the cases are summarised in Table 1.

The 2 most frequent symptoms were dyspnoea (73.9%)

Table 1. Demographic characteristics and co-morbidities of the patients with influenza A (H1N1) virus

Variable	(n = 23)
Age, median (range)	37 (17-82)
Female sex (n) (%)	15 (65.2)
APACHE II score, median (range)	19 (5-39)
BMI, median (range)	26.9 (13-42)
Comorbidity (n)	
Asthma	2
Diabetes	1
Hypertension	1
Congestive heart failure	1
Alzheimer Disease	1
Malignancy	1
Cerebral palsy	1
Sleep apnea syndrome	1
Morbid obesity	1
Pregnancy+postpartum	4+1
Signs and symptoms* (n) (%)	
Dyspnea	17 (73.9)
Fever	16 (69.6)
Cough	14 (60.9)
Myalgias	5 (21.7)
Sore throat	3 (13)
Rhinorrhea	2 (8.7)
Skin eruption	1 (4.3)
Nausea/vomiting	1 (4.3)
Subconjunctival hemorrhage	1 (4.3)
Days from onset of symptoms to ICU admission, median (range)	5 (1-21)
ICU lenght of stay, median (range)	14 (4-119)
ICU mortality, (n) (%)	6 (26.1)

APACHE: Acute Physiology and Chronic Health Evaluation, BMI: Body Mass Index, ICU: Intensive Care Unit
* The patients have more than one symptom.

and fever (69.6%) (Table 1). The time period from the onset of symptoms to ICU admittance was a mean of 5 days (1–21 days). In 14 cases of radiologically confirmed pneumonia, the mean PaO2/FiO2 ratio was 64.5 (46.5–198). There was no statistically significant difference between the surviving patients and the deceased patients in terms of pulmonary radiographic findings, mean PaO2/FiO2 ratios, and laboratory parameters (Table 2).

No bacterial agents known to cause pneumonia were

Table 2. Radiographic findings, oxygenation and laboratory data of the patients with influenza A (H1N1) virus

	All Cases (n=23)	Survivors (n=17)	Nonsurvivors (n=6)	P value
Radiographic findings				
No infiltration (n) (%)	9 (%39.1)	8	1	
Unilateral infiltration (n) (%)	10 (%43.5)	6	4	0.480
Bilateral infiltration (n) (%)	4 (%17.4)	3	1	
Oxygenation median (range)				
PAO_2/FiO_2	64 .5 (46.5-198)	66.5 (46.5-198)	60.6 (51-90.2)	0.431
Laboratory data median (range)				
WBC count(K/μL)	8400 (630-20800)	7480 (1620-20400)	12600 (630-20800)	0.759
Platelet count (K/μL)	222669 (54800-432000	233000 (61700-432000)	166000 (54800-390000)	0.392
Urea (mg/dl)	25 (9-151)	25 (9-151)	39.5 (17-119)	0.759
Creatinine (mg/dl)	0.8 (0.5-2.9)	0.8 (0.5-2.9)	0.75 (0.5-1.9)	0.919
AST (IU)	43 (14-767)	43 (14-767)	68 (24-179)	0.865
ALT (IU)	24 (10-453)	23 (10-453)	25 (10-73)	0.708

WBC: White blood cell. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

found in the routine cultures from endotracheal aspirate samples. All patients received oseltamivir (150–300 mg/day for 10 days) and antibiotherapy. In addition, 10 (43.5%) patients received corticosteroids (Table 3). IMV was administered to 18 (78.3%) patients (12 cases [52.2%] with IMV only, and 6 patients [26.1%] with a transition from NIMV to IMV) for a mean of 8 days (range 4–16 days). The other 5 (21.7%) patients were supported with NIMV only (Table 3).

The mean duration of stay in the ICU was 14 days (4–

Table 3: Characteristics of treatments of the patients with influenza A (H1N1) virus

Characteristic	All Cases (n=23)	Survivors (n=17)	Nonsurvivors (n=6)	P value
NIMV (n) (%)	12 (52.2)	7 (41.2)	5 (83.3)	0.155
IMV (n) (%)	6 (26.1)	6 (35.3)	0 (0)	0.144
NIMV+IMV (n) (%)	5 (21.7)	4 (23.5)	1 (16.7)	1.000
Duration of IMV (day), median (range)	10 (0-119)	6 (0-43)	16.5 (3-119)	0.135
Duration of NIMV (day), median (range)	0 (0-5)	1 (0-5)	0 (0-3)	0.177
Days from onset of symptoms to first oseltamivir dose, median (range)	4 (1-22)	4 (1-22)	4 (2-6)	0.562
Days from onset of symptoms to first antibiotic dose, median (range)	5 (1-22)	6 (1-22)	4 (2-6)	0.431
Duration of antibiotic use, median (range)	5 (1-22)	6 (1-22)	4 (2-6)	0.431
Days from onset of symptoms to steroid median (range)	0 (0-23)	0 (0-23)	5 (0-8)	0.431

IMV: Invasive mechanical ventilation
NIMV: Noninvasive mechanical ventilation

119) for all patients. At the end of the treatment, 17 patients (73.9) survived, and 6 (26.1%) patients died. The mean length of stay in the ICU for surviving patients and deceased patients was 14 days (4–62) and 16.5 days (4–119), respectively. No significant difference was found between the 2 groups in terms of the length of stay in the ICU. The APACHE II scores of the deceased patients (28.5 [16–39]) were higher than those of the survivors (14 [5–28]; p = 0.013) (Table 4). Seven (30.4%) patients had a BMI >30, all of whom were discharged with medication. None of the obese patients died.

Table 4. Characteristics of the patients with influenza A (H1N1) virus

Variable	All Cases (n=23)	Survivors (n=17)	Nonsurvivors (n=6)	P value
Age, median (range)	37 (17-82)	37(17-81)	35.5(25-82)	0.812
Female sex (n) (%)	15 (65.2)	12(70.6)	3(50)	0.621
APACHE II score, median (range)	19 (5-39)	14(5-28)	28.5(16-39)	0.013
Days from onset of symptoms to ICU admission, median (range)	5 (1-21)	6(1-21)	4(2-7)	0.473
ICU lenght of stay, median (range)	14 (4-119)	14(4-62)	16.5(4-119)	0.812

APACHE: Acute Physiology and Chronic Health Evaluation,
ICU: Intensive Care Unit

No statistically significant difference was observed in terms of demographic and laboratory data between those who received corticosteroids and those who did not. Corticosteroid use also had no effect on survival.

When risk factors affecting mortality were examined with logistic regression analysis, co-morbidity was found to be a factor that influenced patient mortality (p = 1.000). The variables of the APACHE II score (p = 0.999), laboratory values (leucocytes, p = 0.997; thrombocytes, p = 0.997; urea, p = 0.999; creatinine, p = 1.000; aspartate aminotransferase, p = 0.995; alanine aminotransferase, p = 0.998), pulmonary radiograph findings (p =0.994), steroid use (p = 0.997), and the length of ICU stay (p = 0.998) were not found to be significant (logistic model significance, p = 0.009).

Discussion

We conducted a retrospective study of cases with severe H1N1 virus infection who were treated in the ICU for respiratory failure from November 2009 to February 2010. We aimed to describe the demographic characteristics, clinical features, and outcome of adult patients with this condition.

The cases examined in this study represent a population affected by a pandemic. Patients infected with pandemic H1N1 influenza A virus were determined to be of a younger age than patients infected with the seasonal influenza virus. It has been suggested that patients >60 years of age may be immune to the H1N1 virus or previous infection with influenza virus which has similar antigenic structures[9,14,15]. Nin et al.[9] reported that only 7% of patients diagnosed with H1N1 infection and admitted to the ICU were >65 years of age. Other studies that have reported the patient age to be 27–44 years support this finding[6,7,11,12,15,16]. Our data also confirmed that the majority of patients infected with H1N1 were young adults.

The majority of the patients with H1N1 infection had a risk factor such as a co-morbidity or were pregnant[5,6,8,9,12,14-17]. In the current study, 60.9% of cases had an accompanying risk factor, which is a similar finding in previously mentioned studies. In addition to chronic disease and immunosuppression, the risk of H1N1 influenza infection increases during pregnancy[2,5,18-21]. In a study of pregnant women with serious influenza infection conducted in Australia, the relative risks of hospitalisation, admittance to ICU, and death were determined to be 5.2, 6.5, and 1.4, respectively[23]. Louie et al.[15] reported that of the 20% of hospitalised pregnant women requiring admittance to ICU, the majority were in the second or third trimester. In the current study, 4 pregnant women and 1 postpartum patient were admitted to the ICU. During the treatment period, all 4 infants were delivered by Caesarean section. At the end of the treatment, 1 patient died.

Obesity is a newly defined risk factor that may have contributed to the mortality in the 2009 H1N1 Influenza A pandemic[3,10,22,23]. As obesity rates are high in severe H1N1 cases requiring ICU treatment, and obesity creates a risk for H1N1 infection, researchers have suggested that it may be diabetes mellitus and cardiovascular diseases together with obesity that increase the risk of mortality[2,23,24]. Although obesity has been defined as a risk for the development of pneumonia, there are researchers who do not agree with this assessment[8]. In the current study, 7 patients had a BMI >30 and all were alive at the end of the treatment.

The symptoms of H1N1 infection are similar to those of seasonal influenza (high temperature, cough, sore throat, runny nose, headache, and myalgia)[2,7,10,16,17,25]. In a study by Perez-Padilla et al.[26], the most frequently seen symptoms were reported to be fever, cough, and other respiratory problems. Kumar et al.[8] determined that the most common symptoms were those affecting the respiratory system, weakness, and muscle pain. In the current study, the most frequently seen symptoms were cough, fever, and dyspnea.

Previous studies of H1N1 infected patients with acute respiratory symptoms have shown infiltration rates of 31.8%–100% based on pulmonary radiographs[8,9,24]. In the current study, although all the patients were admitted to ICU with respiratory problems, 60.9% were determined to have unilateral or bilateral infiltrations. There were no significant findings related to the pulmonary radiograph screens of the remaining patients (39.1%) during hospitalisation.

The use of neuroaminidase inhibitors is recommended in cases of proven or suspected H1N1 infection[3]. A study by Louie et al.[15] reported starting antiviral treatment within 48 hours of the onset of symptoms. Poeppl et al.[2] reported the use of oseltamivir in 70.8% and Dawood et al.[27] in 74% of cases. Oseltamivir was used in all cases in the current study. This was because of the outbreak reaching our country later than other countries and the availability of results from published medical articles relating to the effectiveness of this antiviral agent. While the duration from the onset of symptoms to starting treatment was reported as 1.5 days by Louie et al.[15], this period was 4 days in the current study. This delay may be due to late presentation at the hospital by patients following the onset of symptoms.

In addition to antiviral therapy, antibiotherapy has been widely applied to cases of H1N1 infection[8,14,28]. Jain et al.[14] determined that 79% of patients presenting at the hospital received antibiotherapy and of these patients, 70% used more than one antibiotic. In that study, it was reported that 3 days passed from the onset of symptoms to presentation at a hospital. Kumar et al.[8] reported a rate of 98.8% for antibiotherapy in cases treated for H1N1 infection in the ICU, with a period of 5 days from the onset of symptoms to admittance to ICU. In the current study, as the period from the onset of symptoms to admittance was determined to be 5 days, antibiotherapy was applied to all cases to cover all typical and atypical pneumonia agents.

The use of corticosteroids for the treatment of critical cases with H1N1 infection in the ICU has come into practice[2,8,17,29-31]. In cases of respiratory impairment associated with serious H1N1 infection, corticosteroid use has been reported as 51%–69%[7,8]. While some researchers have administered corticosteroids to patients with co-morbidities such as chronic obstructive pulmonary disease and asthma[17], others have administered corticosteroids in the early stages of infection to all patients admitted to the ICU with H1N1 infection[30]. It has been suggested that the early stage administration of corticosteroids has not improved prognosis[27] and has even increased the risk of superinfection[30]. In the current study, a dosage of 1 mg/kg of methylprednisolone was administered to 10 (43.5%) patients, and the use of corticosteroids was determined to have had no effect on mortality.

Limitation.

Firstly, the study was conducted retrospectively. Secondly, because the patients examined in the studies were limited to those in our centre only, the sample size was small, and this could affect the conclusions drawn from the study.

Conclusion

When compared to reports in the literature, the demographic, epidemiological, and clinical characteristics of the patients in those studies were similar to the patients in our study. Patient mortality was high despite the use of appropriate antiviral and antibiotic treatment. We believe that the high mortality rate may be related to the higher APACHE II scores during admission to the ICU, and to the delayed antiviral treatment and mechanical

ventilation support due to late admission to hospital. The pandemic influenza A H1N1 virus should be considered in the differentiation of community-acquired pneumonia, especially in younger patients presenting with severe pneumonia and who need mechanical ventilation.

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