

## Are we Prepared to Future Flu Pandemics? Experiences in Hospitalized Patients with 2009 H1N1/A Influenza

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### Abstract

**Background:** Pandemic H1N1 influenza virus is a cause of a wide spread out break of febrile respiratory infection in Turkey and worldwide. We describe the characteristics of patients who were hospitalized with H1N1/A influenza in Dicle University, Diyarbakir, Turkey from October 2009 to mid-November 2009.

**Methods:** We collected data of 36 patients who were hospitalized for at least 3 days for influenza-like illness and who were positive for the H1N1/A virus using by real-time reverse-transcriptase-polymerase-chain-reaction assay.

**Results:** Of the 36 patients we studied, 17% were admitted to an intensive care unit and 8% died. Seven-teen percent of the patients were children under the age of 18 years, but never were 45 years of age or older. Eighty percent of the patients had at least one underlying medical condition; these conditions included asthma, chronic obstructive pulmonary disease; diabetes; lung, heart, and neurologic diseases; and pregnancy. All of the patients who underwent chest radiography on admission, 28 (78%) had findings consistent with pneumonia. Three (8%) of the patient were died. The median age of patients who died (29.6 years) was not significantly higher than that of the non-fatal cases (26.5 years,  $p > 0.05$ ). Of the 36 patients for whom data were available regarding the use of antiviral drugs, such therapy was initiated in 26 patients (72%) at a median of 3 days after the onset of illness.

**Conclusions:** During of the 45 daily period, H1N1/A influenza caused severe illness requiring hospitalization, including pneumonia and death. Nearly three quarters of the patients had one or more underlying medical conditions. One severe illnesses were reported among person with pregnancy. Patients seemed to benefit from antiviral therapy. Data suggest that the use of antiviral drugs was beneficial in hospitalized patients, especially when such therapy was initiated early.

**Keywords:** H1N1/A influenza; Young adult; Underlying disease

### Introduction

Pandemic influenza A (H1N1) virus has an envelope and negativesense segmental RNA genome. This virus which is a member of the orthomyxoviruses has segmental structure of RNA. Due to segmental structure of RNA, mutation and reassortment of the gene segment, have been frequently seen among different human and animal strains of this virus. Several pandemics of the influenza A virus have been encountered at intervals of 10 to 50 years since the beginning of the 19<sup>th</sup> century worldwide. Spanish pandemic influenza H1N1 in

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1918-1920, Asian influenza H2N2 in 1957-1958, and Hong Kong influenza H3N2 in 1968-1969 were some pandemics that affect the people of the world [1]. In April 15 and April 17, 2009 a pandemic influenza A (H1N1) virus was investigated from two epidemiologically unrelated patients in the United States [2]. This virus had gene segments from human, swine, and avian strains [2,3]. It was detected that 2 of the polymerase components (PB2 and PA genes) have been originated from an avian virus, 1 (PB1) from the human H3N2, hemagglutinin (HA), nucleoprotein (NP), and nonstructural (NS) genes originated from the classical swine virus, and neuraminidase (NA) and matrix/membrane proteins (M) genes from Eurasian swine virus [4]. The virus had ability of human-to-human transmission. At that time, pandemic influenza A (H1N1) virus infections spread worldwide and also in Turkey. Patients from more than 207 countries around the world and more than 8,768 deaths were reported, up to the 48<sup>th</sup> week of 2009 [1]. According to reports of World Health Organization (WHO), the highest mortality was observed in Americas (5,878 deaths) followed by Europe (918 deaths), SouthEast Asia (766 deaths), Western Pacific (706 deaths), the Eastern Mediterranean (392 deaths), and Africa (108 deaths) [5]. In Turkey, after the first reported laboratory-confirmed human case on May 15, 2009, the influenza infections increased, continuously [1,6]. With the beginning of education period, epidemics were observed in various elementary schools and the number of laboratory-confirmed cases reached more than 9,500 in Turkey [1,6]. Nasopharyngeal and/or nasal swabs of all Turkey cases suspected with pandemic influenza A (H1N1) virus infection were sent to one of the following laboratories: Refik Saydam National Public Health Agency (RSNPHA), National Influenza Center in Ankara, National Influenza Reference Laboratory at Istanbul University, and regional public health laboratories [1]. A total of 36 cases whose clinical samples confirmed by Real-time molecular analysis assay as influenza A (H1N1) were hospitalized in Dicle University Hospital. In this study, we described the clinical characteristics of patients who were hospitalized with H1N1/A influenza in Dicle University, Diyarbakir, Turkey from October 2009 to mid-November 2009 and we aimed to determine how it should be our approach to hospitalized patients in case of a possible outbreak.

### Methods

#### Study design

Dicle University Hospital is the largest health centre in the southeastern region of Turkey, serves approximately three million people, and provides primary, secondary, and tertiary care. Every year, 26,000 patients admit to emergency department of Dicle University Hospital. In 2009, the Flu Clinic was created during the H1N1 Influenza A pandemic to deal with the heightened risk of infection spreading within the hospital. The hospital was also the reference centre for other nearby hospitals. A retrospective study conducted to collect the epidemiological data of H1N1 Influenza A cases.

#### Patients and samples

A total of 36 patients who were hospitalized for at least 3 days for influenza-like illness from October 2009 to mid-November 2009 and confirmed for influenza H1N1/A virus by a real-time reverse-transcriptase-polymerase-chain-reaction assay were included in this study. Epidemiological and demographic characteristics of the patients were recorded and evaluated. In this study patients were divided into 2 groups according to their initial treatment time. Patients in the early treatment group (26 patients) received antiviral therapy within three days of the onset of symptoms. Patients in the late treatment group (10 patients) received antiviral therapy five days after the onset of symptoms. Nasopharyngeal specimens of the patients were collected from the patients [7-10]. In this study diagnosis of novel H1N1 is made according to the U.S. Centers for Disease Control (CDC) case definitions [11].

#### Laboratory diagnosis (real-time RT-PCR)

In pandemic period "in-house" real-time PCR protocol provided by CDC was used for detection of influenza A (H1N1) virus. RNA extraction was done with QIAamp viral RNA mini kit (Qiagen, Valencia, CA, USA) or with a High Pure Viral RNA isolation kit from Roche. Real-time RT-PCR was performed on ABI 7000 and/or 7500. NA, HA and M genes of the isolate from the index case were partially sequenced and the resulting sequences were analysed by CLC Main Workbench 4.1.1 Software program (Denmark).

#### Statistical analyses

All statistical analyses were performed using SPSS for Windows 18.0 (IBM, Chicago, IL, USA). P values of  $\leq 0.05$  were considered to be statistically significant. This study was approved by the local ethical committee and written consents were taken from each patient.

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### Results

Of the 36 patients studied, 17% were admitted to an intensive care unit and 8% died. Seventeen percent (17%) of the patients were children under the age of 18 years, but never were 45 years of age or older. Eighty percent (80%) of the patients had at least one underlying medical condition; these conditions included asthma (n:6), chronic obstructive pulmonary disease (n:10); diabetes (n:4); heart failure (n:5), and neurologic diseases (n:2); and pregnancy (n:1). All of the patients who underwent chest radiography on admission, 28 (78%) had findings consistent with pneumonia. Three of the patient were died. The median age of patients who died (29.6 years) was not significantly higher than that of the non-fatal cases (26.5 years,  $p > 0.05$ ). Of the 36 patients for whom data were available regarding the use of antiviral drugs, such therapy was initiated in 26 patients (72%) at a median of 3 days after the onset of illness. In the follow up of 33 patients after treatment was showed that all patients were healed.

### Discussion

In early April 2009, cases of human infection with pandemic influenza A (H1N1) virus were detected in the United States and Mexico. The virus then spread rapidly to other areas of the world and also Turkey [7]. Turkey is a transcontinental Eurasian country. Asian Turkey, which includes 97% of the country, is separated from European Turkey by the Bosphorus, the Sea of Marmara, and the Dardanelles [8]. Turkey is divided into seven census regions: Marmara, Aegean, Black Sea, Central Anatolia, Eastern Anatolia, Southeastern Anatolia and the Mediterranean [8]. Turkey's geographical features and climatic characteristics vary by the regions. For this reason type and frequency of infections also vary according to the regions. Southeastern Anatolia is a region of more than 7 million people live and human population consists of 40% 0-15 years old children, 54% 15-65 and remaining 6% > 65 age group. To our knowledge, there were few data on the pandemic influenza A (H1N1) in this region. For this reason we thought that the evaluation of hospitalized cases with influenza A (H1N1) should be beneficial for world literature.

Influenza pandemics of the past century have been related with consistent epidemiologic curve, with peaks in the spring, fall, and later winter [9]. The studies of 2009 influenza A (H1N1) reported that this disease generally affected young patient group with the mean age of patients ranging from 20 to 25 years old [2,9]. According to the literature the low median age of 2009 influenza A (H1N1) were different from those for seasonal influenza and SARS, in which older patients appear more susceptible to severe disease [9,10]. In our study 18 % of the patients were children under the age of 18 years, but never were 45 years of age or older. Many studies reported that a significant portion of cases was in the young adult group [1,2,11,12]. The lower attack rate of pandemic influenza A (H1N1) virus infections in older people may be associated with the presence of a crossreactive antibody [1]. Serologic studies reported that 2009 influenza A (H1N1) is anovel influenza strain with little protection afforded by seasonal influenza vaccination. However the authors suggested that adults older than 60 years appear to have some preexisting immunity to this virus [9]. The World and Turkey data showed that gender was not a risk factor for acquisition of 2009 influenza A (H1N1) infection and mortality. Ertek., *et al.* [1] also demonstrated that there were no statistically significant differences between the PCR positivity rates obtained in males and females [13,14].

The case-fatality rate in previous influenza pandemics has varied widely. The Spanish flu of 1918 caused 50 million deaths in 500 million individuals infected (10% case-fatality rate), while the Hong Kong flu of 1968-1969 caused 33,000 deaths among 50 million infected (0.1% case-fatality rate). The case-fatality rate of avian influenza A (H5N1) was in the range of 14% to 33% [9,15-18]. The World Health Organization reported that 254 206 cases of 2009 influenza A (H1N1) and 2837 deaths August 30, 2009 (case-fatality rate was approximately 1% for influenza A(H1N1)). In a large-scale California study, Louie., *et al.* [12] found that overall fatality was 11% and was highest (18%-20%) in persons aged 50 years or older. In our study the median age of patients who died (29.6 years) was not significantly higher than that of the non-fatal cases. However, we suggested that case-fatality rate was related with many factors such as the number of people living in an area, age distribution of population, the quality of hospital and intensive care services and underlying disease of patients. In current study 17% of patients were admitted to an intensive care unit and 8% died and 78% had findings consistent with pneumonia. Similarly, studies showed that respiratory tract disorders are commonly seen in influenza A (H1N1) cases. In a study, Domínguez-Cherit., *et al.* [9] reported that fever and respiratory symptoms were harbingers of disease in all cases and they

suggested that there was a relatively long period of illness prior to presentation to the hospital, followed by a short period of acute and severe respiratory deterioration. In their study, within 60 days, 41% of critically ill patients had died. Louie, *et al.* [12] reported that 66% of patients had infiltrates on chest radiographs and 31% required intensive care and the most common causes of death were viral pneumonia and acute respiratory distress syndrome. In a Turkey study of 15 cases and 4 cases needed intensive care monitoring and 2 of them died (12.5%) because of severe respiratory insufficiency [7]. Therefore, we thought that special attention should be given in treatment of patients with pneumonia during pandemics and these patients should be hospitalized in intensive care unit. On the other hand, according to Advisory Committee on Immunization Practices, individuals with risk factors for severe complications from seasonal influenza such as chronic lung disease, immunosuppression, and pregnancy, also at risk of severe illness from pandemic 2009 influenza A (H1N1) infection [2,19,20]. Many studies reported that pneumonia, bacterial coinfection, and exacerbation of underlying medical conditions, such as congestive heart failure were complications of influenza A (H1N1) infection [21-24]. A study of 2009 influenza A (H1N1) infection in pregnant women reported that patients with late gestational age, the presence of co-morbid disease, and multiple pregnancy had poor prognosis [7]. In our study 80 % of the patients had at least one underlying medical conditions such as asthma, chronic obstructive pulmonary disease; diabetes, heart, and neurologic diseases; and pregnancy. However the limitation was the low number of patients included in the study.

Early antiviral-therapy with NA inhibitors are important for controlling influenza A (H1N1) virus pandemics. Pandemic influenza A (H1N1) strains were known generally susceptible to NA inhibitor but resistant to adamantane [1,25,26]. However up to December 11, 2009, a total of 102 oseltamivir-resistant isolates were detected from many countries [1,25,27,28]. In some of the regions of the world, resistance to antiviral drugs did not detect [29,30]. Molecular studies indicated that all pandemic influenza A (H1N1) viruses in Turkey were susceptible to oseltamivir [1]. In present study, of the 36 patients for whom data were available regarding the use of antiviral drugs, such therapy was initiated in 26 patients (72%) at a median of 3 days after the onset of illness and all of these people improved. This result suggested that the early use of antiviral drugs was beneficial in hospitalized patients. On the other hand, it was reported that some mutations at position H275Y could cause oseltamivir resistance and there was a possibility of transmission of the resistant isolates to other patients. In addition patients having prolonged postexposure prophylaxis or treatment with subtherapeutic dosages were reported at risk of developing resistance to oseltamivir [31,32].

### Conclusion

In conclusion, pandemic influenza A (H1N1) viruses generally affected young patient group. Underlying medical conditions such as asthma, chronic obstructive pulmonary disease; diabetes mellitus, and pregnancy have negative effects on the course of the disease and pneumonia is the most common causes of deaths. This study revealed that special attention should be given in treatment of patients with pneumonia and underlying diseases during pandemics and these patients should be hospitalized or if necessary these patients should be taken to intensive care unit. In addition this study demonstrated that the use of antiviral drugs was beneficial in hospitalized patients, especially when such therapy was initiated early. Based on our experiences, we can say that, the microbiologists play an important role in the control of influenza pandemics and molecular methods should be beneficial for determining of type and drug resistance of virus. Providing free seasonal influenza vaccine for risk groups is necessary for community's health.

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