



Clinical manifestations, therapy and outcome of pandemic influenza A (H1N1) 2009 in hospitalized patients

Kliničko ispoljavanje, terapija i ishod pandemijskog gripa A (H1N1) 2009 kod hospitalizovanih bolesnika

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Abstract

Background/Aim. Increasing number of epidemiological and clinical studies to date showed that the pandemic influenza A (H1N1) 2009, by its characteristics, significantly differs from infection caused by seasonal influenza. Therefore, the information about clinical spectrum of manifestations, risk factors for severe form of the disease, treatment and outcome in patients with novel flu are still collected. **Methods.** A total of 98 patients (mean age 32 ± 15 years, range 14–88 years) with the signs and symptoms of novel influenza were treated in the Clinic for Infectious and Tropical Diseases, Military Medical Academy. There were 74 (75.5%) patients with suspected influenza A (H1N1) 2009, 10 (10.2%) with the likelihood and 14 (14.3%) with the confirmed influenza. In all the patients we registered the basic demographic data, risk factors for severe disease, symptoms and signs of influenza, laboratory tests and chest radiography. We analyzed antiviral therapy use and disease outcome (survived, died). **Results.** The average time from the beginning of influenza A (H1N1) to the admission in hospital was 3 days (0–16 days) and from the moment of hospitalization to the Intensive Care Unit (ICU) admission was 2 days (0–5 days). There were 49 (50.0%) patients, 20–29 years of age and 5 (5.1%) patients older than 65. A total of 21 (21.4%) patients were with underlying disease, 18 (18.4%) were obese, 19 (19.4%) were cigarette smokers. All of the patients had fever, 81 (82.6%) cough, while dyspnea and diarrhea

were registered in 1/4 of the patients. In more than 75% of the patients laboratory tests were within normal limits. The real-time polymerase chain reaction (PCR) test for identification of influenza A (H1N1) 2009 was positive in 14 (77.8%), while pneumonia was verified in 30 (30.7%) of the patients. Six (6.1%) patients, mean age of 45 ± 14 years (31–59 years) were admitted to the ICU, of whom five (5.1%) had Adult Respiratory Distress Syndrome (ARDS). Risk factors were registered more frequently in the patients with acute respiratory failure (14.2% vs 4.9%, $p < 0.05$). A total of 67 (68.4%) patients received oseltamivir, 89 (90.1%) was applied to antibiotics and 64 (65.3%) were treated with a combined therapy. Antiviral therapy was applied to 43 (43.3%) patients in the first 48 hours from the onset of the disease, of whom only one (3.4%) developed ARDS. Fatal outcome was noted in 2.0% of the patients (2 of 98 patients) and in 33.3% of the patients treated in the ICU. **Conclusion.** Novel influenza A (H1N1) is most commonly manifested as a mild acute respiratory disease, which usually affects young healthy adults. A small number of the patients develop severe illness with acute respiratory failure and death. Patients seem to have benefit from antiviral therapy especially in first 48 hours.

Key words: influenza A virus, H1N1 subtype; disease transmission, infections; disease progression; drug therapy; mortality.

Apstrakt

Uvod/Cilj. Više epidemioloških i kliničkih studija do sada pokazalo je da se pandemijska influenza A (H1N1) 2009 po svojim karakteristikama značajno razlikuje od infekcije izazvane virusom sezonske influence. Zato se i dalje prikupljaju in-

formacije o kliničkom spektru ispoljavanja, faktorima rizika od težih oblika bolesti, terapiji i ishodu kod obolelih od novog gripa. **Metode.** U Klinici za infektivne i tropske bolesti Vojnomedicinske akademije lečeno je 98 bolesnika sa novim gripom, prosečne starosti 32 ± 15 godina (14–88 godina). Broj bolesnika sa sumnjom na grip A (H1N1) 2009 bio je 74

(75,5%), sa verovatnim gripom 10 (10,2%), a sa potvrđenim gripom 14 (14,3%). Kod svih bolesnika registrovani su osnovni demografski podaci, faktori rizika od težeg oblika bolesti, simptomi i znaci gripa, laboratorijski nalazi i radiografija grudnog koša. Analizirana je primenjena antivirusna terapija i ishod bolesti (preživeli, umrli). **Rezultati.** Prosečno vreme od početka gripa A (H1N1) 2009 do prijema u bolnicu bilo je 3 dana (0–16 dana), a do prijema u jedinicu intenzivne nege (JIN) 2 dana (0–5 dana). U životnom dobu od 20–29 godina bilo je 49 (50,0%) bolesnika, a ≥ 65 godina 5 (5,1%) bolesnika. Osnovne bolesti imao je 21 (21,4%) bolesnik, gojaznih je bilo 18 (18,4%), pušača cigareta 19 (19,4%). Povišenu telesnu temperaturu imalo je svih 98 bolesnika, kašalj 81 (82,6%), dispneju i dijurealni sindrom $\frac{1}{4}$ bolesnika. Više od 75% bolesnika imalo je laboratorijske nalaze u granicama normale. *Real-time polymerase chain reaction* (PCR) test za identifikaciju virusa influenza A (H1N1) 2009 bio je pozitivan kod 14 (77,8%) bolesnika. Pneumonija bila je verifikovana kod 30 (30,7%) bolesnika. U JIN bilo je primljeno 6 (6,1%) bolesnika, prosečne starosti

45 ± 14 godina (31–59 godina), od kojih je akutni respiratorni distres sindrom (ARDS) imalo 5 (5,1%). Faktori rizika registrovani su češće kod bolesnika sa akutnom respiratornom insuficijencijom (14,2% prema 4,9%, $p < 0,05$). Oseltamivir je dobijalo 67 (68,4%), antibiotike 89 (90,1%), a kombinovanu terapiju 64 (65,3%) bolesnika sa novim gripom. U prvih 48 sati od početka gripa oseltamivir bio je primenjen kod 43 (43,3%) bolesnika, od kojih je samo jedan (3,4%) razvio ARDS. Smrtni ishod zabeležen je kod 2,0% bolesnika (2 od 98 bolesnika), odnosno kod 33,3% bolesnika lečenih u JIN. **Zaključak.** Novi grip ispoljava se uglavnom kao blaga akutna respiratorna bolest, od koje najčešće obolevaju mlađe odrasle osobe. Mali broj bolesnika razvija teške forme bolesti. Antivirusna terapija može biti od velike koristi, posebno kada se sa njenom primenom otpočne u prvih 48 sati od početka bolesti.

Ključne reči:
grip A virus, podtip H1N1; bolest, prenošenje; bolest, progresija; lečenje lekovima; mortalitet.

Introduction

The first two cases of swine flu in humans, caused by a pandemic strain of influenza A (H1N1), originating from pigs were registered in the territory of the United States in April 2009.^{1,2} In the same period epidemic occurrence of acute respiratory illness caused by new flu virus was recorded in Mexico.³ In just two months the virus spreaded to every continent and most countries in the world, so that the World Health Organization declared the first pandemic of the 21st century on 11th June 2009.^{4–10} In these circumstances it was the matter of time when the new strain of influenza A (H1N1) virus would occur in Serbia. One of the events in 2009 which was considered as the event of high risk for virus entry into Serbia was the Universiade in Belgrade held in July 1–14, 2009. Since the Military Medical Academy (MMA) was responsible for health care status in the participants in the Universiade, the first cases of new influenza patients were treated in the Clinic for Infectious and Tropical Diseases of MMA, just during the event. Despite the occurrence of sporadic cases of the disease during July, the epidemic occurrence of pandemic flu in Serbia began in November 2009.

Unique genetic and antigenic properties of new influenza virus A (H1N1) resulted in a high incidence of infection in the U.S. and other countries. It is estimated that during the pandemic of new influenza A (H1N1), in a period from April 2009 to April 2010, across the U.S. between 43 and 89 million people were infected with the virus, resulting in approximately 274,000 hospitalizations and 12,470 deaths associated with the novel flu virus^{11–15}. Information about the clinical spectrum of manifestations, risk factors for the severity of disease, treatment and outcome in patients with influenza A (H1N1) are still being collected, although a few clinical studies were published on this issue in the past year^{13–26}. Some of these studies indicate that the most serious form of swine flu, which are accompanied by severe hy-

poxemia, multiple organ failure, septic shock, prolonged mechanical ventilation and death are often recorded in young, previously healthy adults^{18–26}.

The aim of this study was to investigate clinical symptoms, risk factors for severe forms of influenza, treatment and outcome in patients with novel influenza A (H1N1) hospitalized in the Clinic for Infectious and Tropical Diseases MMA.

Methods

During a pandemic influenza A (H1N1) 1,288 patients with symptoms and signs of flu-like illness were treated in the Clinic for Infectious and Tropical Diseases, MMA. Out of that number, 98 (7.6%) hospitalized patients were included in this study. There were 68 (69%) men and 30 (31%) women. A total of 52 (53.1%) were the members of the Serbian Army and 46 (46.9%) had health insurance by other institution. Six (6.1%) patients were participants in the Universiade in July 2009, they were sporadic, imported cases of swine flu, while 92 (93.9%) were the patients hospitalized during the period from November 5th 2009 to January 20th 2010, when novel flu assumed a character of an epidemic in Serbia. The average age of the hospitalized patients was 32 ± 15 years (14–88 years). In the first group it was 22 ± 2 years (20–24 years), and the second 33 ± 16 years (14–88 years), which was a statistically significant difference ($p < 0.05$).

The criteria for hospitalization of patients with clinical signs of flu-like illness were: body temperature $\geq 38.0^\circ\text{C}$, findings of pulmonary infiltrates on chest radiography, hypoxemia, acute lung injury ($\text{pO}_2/\text{FiO}_2 < 300$), acute respiratory failure (ARF), hemodynamic instability and dysfunction of other organs, myositis and encephalitis, as well as the existence of predisposing chronic diseases and comorbid conditions (risk factors for severe forms of influenza), such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, chronic cardiovas-

cular disease, chronic kidney disease, epilepsy, neoplasms, immunosuppressive therapy, extreme obesity, second and third trimester of pregnancy and the age over 65 years.

In all of the patients, in addition to the basic demographic data, we registered the presence of predisposing diseases and conditions for more severe disease symptoms and signs of influenza. Laboratory tests were performed (complete blood count, C-reactive protein, urea, creatinine, transaminases, creatine kinase, lactate dehydrogenase, and, if necessary, gas analysis and other laboratory findings). In addition, all the patients on admission underwent chest radiography at the Institute of Radiology, MMA. We used the real-time polymerase chain reaction (PCR) to identify the virus A (H1N1) 2009 from nasopharyngeal swabs of the hospitalized patients. The test was performed in a reference laboratory in the Institute of Immunology and Virology "Torlak". Detection of antibodies against influenza A viruses in paired sera was performed by a complement fixation reaction (CFT), which like other necessary microbiological analyses was performed in the Institute of Microbiology, MMA. The diagnosis of viral or bacterial pneumonia was based on physical findings in the lungs, laboratory findings and radiographic infiltrates in the lung parenchyma. The diagnosis of acute respiratory distress syndrome (ARDS) was based on clinical findings of the acute respiratory infection (ARI), massive bilateral pneumonia on chest radiography, the absence of heart failure and the relationship of partial pressure of oxygen (pO_2) and a fraction of oxygen in inspired air (FiO_2).

Dyspnea and the presence of infiltrates in the lung parenchyma were the key criteria for the introduction of antiviral therapy, but we respected the recommendations of the Center for Disease Control (CDC) and some authorities for treatment of seasonal and pandemic influenza^{27–29}. Antibiotic and antiviral therapies were analyzed in all the patients, as well as the response to the therapy and the final outcome (survived/died).

Body Mass Index (BMI – weight in kilograms divided by body surface area in m^2), was determined to assess the degree of obesity in the patients. The patients with BMI > 30 kg/m^2 were classified as obese, while those with BMI > 40 kg/m^2 were classified as extremely obese. Smoking cigarettes was registered among other potential risk factors for severe forms of influenza.

The Intermediate Care Unit in the Clinic for Infectious and Tropical Diseases, MMA, was adapted to the Intensive Care Unit (ICU) during preparation for pandemic of swine flu including a daily anesthesiologist duty, to establish an effective communication between a specialist in infectious diseases and an anesthesiologist and to separate patients with influenza requiring mechanical ventilation from seriously ill in the ICU.

The results were presented as numbers, percentages and mean \pm SD. The χ^2 test to assess the significance in differences between the groups was used. Probability level of $p < 0.05$ was considered statistically significant.

Results

The average time from the occurring the first symptoms of novel influenza A (H1N1) to hospitalization in our series of patients was 3 days (0–16 days). Average time from the beginning of flu to hospitalization of patients with acute respiratory failure (ARF) was 5 days (1–7 days), while average time from hospital admission to admission in the ICU was 2 days (0–5 days). In 28 (28.6%) patients, average age of 21 ± 6 years (16–37 years) the main criterion for admission was fever ($\geq 38.0^\circ C$). A total of 15 (15.3%) patients were over 50, and only 5 (5.1%) over 65. It was shown that 50% of all the hospitalized patients were 20 to 29. The number of these patients as compared to the number of the patients in other age groups was significantly higher ($p < 0.01$) (Table 1).

Table 1

Age of 98 hospitalized patients with novel influenza

A (H1N1)	
Age (years)	% of patients
10–19	12
20–29	50*
30–39	14
40–49	8
50–59	8
≥ 60	7

* $p < 0.01$ as compared to other age groups

Totally 21 (21.4%) of the patients were with predisposing chronic diseases for the development of severe clinical symptoms of influenza A (H1N1), of whom five patients had ≥ 2 risk factors. Chronic cardiovascular diseases were noticed in 8 (8.2%) of the patients, diabetes mellitus in 6 (6.1%), asthma and COPD in 5 (5.1%) and a long-term immunosuppressive therapy in 4 (4.1%) of the patients. Among the hospitalized patients there was one (1.0%) pregnant woman in the second trimester of pregnancy. In addition, among the hospitalized patients 18 (18.4%) were obese, and 2 (2.0%) extremely obese. A total of 19 (19.4%) patients were cigarette smokers.

Figure 1 shows that the majority of patients demonstrated clinical symptoms and signs of general infectious syndrome, characteristic for influenza. All of 98 patients had

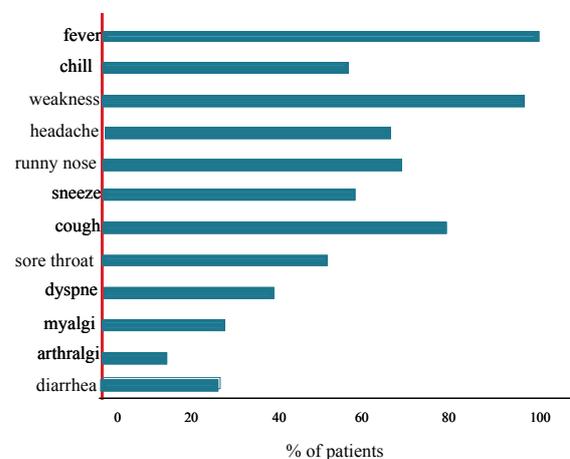


Fig. 1 – The signs and symptoms of novel influenza A (H1N1) in 98 hospitalized patients

fever, fatigue was registered in 94 (95.9%), chills in 60 (61.2%) and headache in 65 (66.3%) of the patients. Myalgia, arthralgia, and symptoms of gastrointestinal tract were recorded in less than ¼ of the patients. Most patients manifested more or less pronounced symptoms and signs of the respiratory tract, and cough was registered in 81 (82.6%), sore throat, runny nose and sneezing in about 60% of the patients, while dyspnea in ¼ of the patients.

Most patients (> 75%) with new influenza A (H1N1) in our series had laboratory findings within the limits of normal. As shown in Figure 2 anemia and leukopenia were registered in 15 (15.3%), while leukocytosis was noted only in 7 (7.1%) of the patients, and thrombocytopenia in 17 (17.3%) of the patients. Monocytosis was found in a total of 20 (20.4%) of the patients. Elevated serum enzymes were found in less than ¼ of the patients, LDH in 23 (23.5%), ALT in 12 (12.2%), GGT in 7 (7.1%) and CK in 20 (20, 4%) of the patients.

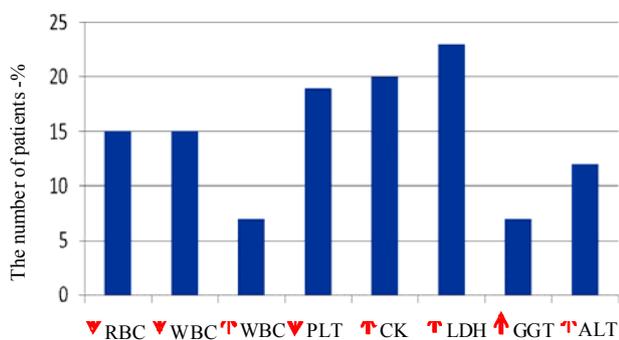


Fig. 2 – The laboratory findings in 98 hospitalized patients with novel influenza A (H1N1)

RBC – red blood cells; WBC – white blood cells; PLT – platelets; CK – creatine kinase; LDH – lactic acid dehydrogenase; GGT – gamma-glutamyl transaminase; ALT – alkaline phosphatase

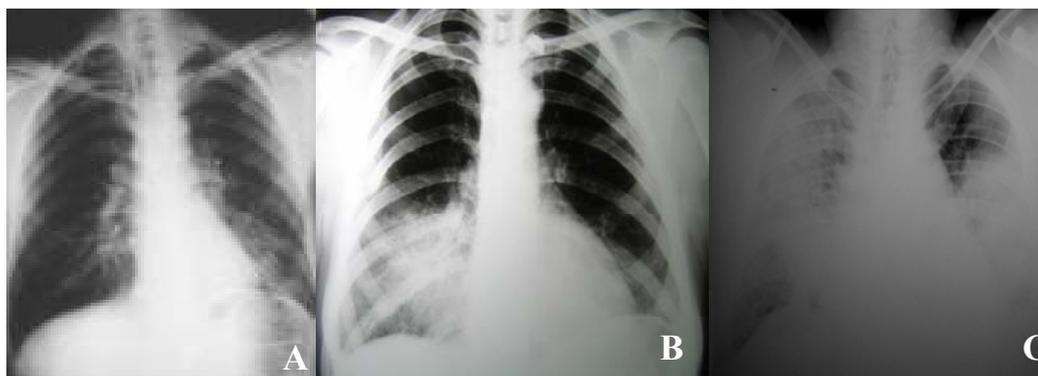


Fig. 3 – Radiographic findings in three patients with novel influenza A (H1N1)
A – viral pneumonia; B – Bacterial pneumonia; C – Adult Respiratory Distress Syndrome (ARDS)

The real-time PCR test for identification of influenza A (H1N1) was performed in only 18 patients due to technical reasons. It was positive in 14 (77.8%) of the patients, while the complement fixation tests (CFT) for the detection of antibodies against influenza A viruses was done in 19 patients, but quadruple increase in titer was registered in 10 (52.6%) of them. There were 74 (75.5%) patients with suspected novel influenza A (H1N1), 10 (10.2%) with a likelihood and

14 (14.3%) with confirmed influenza. All of them were treated for novel pandemic influenza.

In 50 (51.0%) patients novel flu manifested as acute upper respiratory tract infections (rhinitis, pharyngitis, laryngitis), in 18 (18.3%) patients as acute bronchitis, and 30 (30.7 %) patients had radiologically verified pneumonia (Figure 3). Among the patients with risk factors for severe influenza pneumonia was registered in 8 (38.1%) of 21 patients, and among those without risk factors in 22 (28.6%) of 77 patients which was not a statistically significant difference.

Unilateral pneumonia was registered in 15 (15.3%) of the patients, bilateral pulmonary infiltrates in 10 (10.2%) of the patients, and ARDS in 5 (5.1%) of the patients with novel influenza. Acute respiratory failure had a total of 7 (7.1%) patients, six of them admitted to the ICU. The average age of patients with pneumonia was 28 ± 19 years (14–59 years).

Six (6.1%) patients with clinical signs of swine flu and ARI, mean age 45 ± 14 years (31–59 years) were admitted to the ICU. Five of them with clinical signs of ARDS were treated with invasive mechanical ventilation, while one patient met criteria for acute lung injury and was treated with noninvasive mechanical ventilation. Among the patients with ARF, risk factors for developing severe forms of influenza had 14.2% (3 of 21) of the patients, and no risk factors was confirmed in 4.9% (3 of 77) of the patients. This difference was statistically significant ($p < 0.05$). Concerning the occurrence of ARDS in these two groups, the ratio was even more pronounced (14.2% vs 2.6%, $p < 0.01$). Sepsis was registered in two (2.0%), and multiorgan dysfunction in one (1.0%) of the patients. In these patients, *Staphylococcus aureus*, *Acinetobacter* spp and *Pseudomonas aeruginosa* were isolated from blood cultures.

Antiviral therapy, oseltamivir 150 mg per day orally, was prescribed to 67 (68.4%) of the patients, of whom 64 (65.3%) received antibiotic therapy at the same time, and 3 (3.1%) patients were treated only with oseltamivir. In the group of patients treated with a combination of therapies 31 (31.6%) patients received oseltamivir and azithromycin, and 33 (33.7%) oseltamivir, azithromycin and ceftriaxone.

Antiviral therapy was prescribed in all 67 patients after admission to the clinic, and the average time from the onset of symptoms to the initiation of the therapy was 2.6 days (0–12 days). The application of oseltamivir in the first 48 hours after the beginning of novel flu was started in 29 (43.3%) patients, among whom only one (3.4%) developed ARDS. Oseltamivir was given to 38 (56.7%) patients 48 hours after the onset of flu, of whom 4 (10.5%) had ARDS. The appearance of ARDS among the patients who received oseltamivir after 48 hours from the start of flu was three times higher, compared to the first group, but the difference was not statistically significant.

Antibiotic therapy (ceftriaxone 2 g daily, intravenously, and azithromycin 500 mg daily, orally) was administered to 89 (90.1%) of the patients with novel influenza. Only antibiotics (without antiviral drugs) were administered to 25 (25.5%) of the patients, azithromycin to 20 (20.4%), ceftriaxone to one (1.0%), and azithromycin combined with ceftriaxone to 4 (4.1%) the patients.

Six (6.1%) of the patients were treated only with symptomatic therapy.

Fatal outcome was noted in 2 (2.0%) of 98 patients (33.3% of patients treated in the ICU). Risk factors for severe forms of influenza had an impact on the outcome of the disease, which can be illustrated by the example of two patients at the age of 41 years. The first patient who died had arterial hypertension, was extremely obese and heavy smoker, while another one, who survived, had no risk factors. In the first patient antiviral therapy was included on the sixth day, and in another one on the seventh day from the start of flu. Before the start of the therapy initial ARDS in both patients had already been registered.

Discussion

The study presented a series of 98 patients with novel influenza A (H1N1) who were hospitalized in the Clinic for Infectious and Tropical Diseases, MMA during a 10-week period of an epidemic of influenza in Serbia. The number of male patients was twice as high as the number of women, probably because over 50% of the patients were from the ranks of the Serbian Army. Cui et al.¹⁸ registered a similar ratio of genders in patients with influenza A (H1N1) and pneumonia, but the cause of that relationship was not considered. The clinical features of imported influenza A (H1N1) to the Universiade 2009 participants involved in the study did not differ from the clinical picture in patients during a pandemic, although there was a significant difference in age between the two groups.

The average age of the patients in our study was 32 years, in contrast to 21 years in 272 patients studied by Jain et al.¹⁷, and 27 years in 1,088 patients studied Louie et al.²⁶ This difference was probably because the aforementioned authors included in their research the youngest population of pediatric patients, while the youngest patient in our study was 14 years old. The average age of patients with influenza A (H1N1) treated in the ICU was higher in our than in several other studies. In the study of Jain et

al.¹⁷ it was 29 years, in the study of Kumar et al.²³ (215 critically ill patients) 32 years, and in the study of Davies et al.²⁵, who presented 68 critically ill patients with novel flu it was 34 years. In two other studies the average age of critically ill patients with novel flu was similar to that in this study, so that in the study of Cui et al.¹⁸ it was 41 years, and in the study of Domínguez-Cherita et al.²² it was 44 years. According to the available data it cannot be concluded precisely if the difference in age among the patients treated in ICU in these studies could have an impact on the outcome.

The average time from the beginning of the first flu symptoms to hospitalization of our patients was not significantly different in comparison to some other studies. For example, in the study of Jain et al.¹⁷ it was 3 days (0–18 days), and in the study of Kumar et al.²³ it was 4 days (0–22 days). In our study, the average time between hospital admission and admission to the ICU was 2 days, whereas in the study of Kumar et al.²³ and Domínguez-Cherita et al.²² it was only one day. The conclusion of these authors was that the critical illness caused by influenza A (H1N1) occurs rapidly after admission to hospital, often in young adults and is accompanied by severe ARDS, refractory hypoxemia, shock and high mortality rate. Reasons for the difference in time before admission to the ICU, or to the development of critical illness, cannot be considered correctly because of the lack of information about it, so it remains to be investigated.

Epidemiological characteristics of novel influenza related to hospitalization, severity of disease and mortality rate have been intensively investigated since the start of a pandemic, and so far the results have been very interesting. According to the obtained data, epidemiological profile of novel flu is different from diseases caused by seasonal influenza virus. Pandemic influenza A (H1N1) most commonly affects younger persons and generally causes mild illness, while the most severe form of seasonal influenza usually affects people under the age of 2 years and older than 65 and patients with predisposing diseases or conditions for the development of severe forms of influenza. It is known that in the peak period of disease, hospitalizations are commonly necessary among people over 65 in seasonal influenza and that more than 90% of deaths from seasonal influenza are registered in elderly patients. On the other hand, when it comes to novel influenza, young adults, pregnant women and people with chronic disease pandemic virus infected are at higher risk of hospitalization and the development of severe forms of illness or death^{26, 27, 30–40}.

In our study 50% of the hospitalized patients were in the third decade of life, and only 5% of them had more than 65 years. The difference in affected population could be explained by the fact that young people were more often exposed to novel influenza virus A (H1N1), and that younger febrile persons were more often tested for influenza virus A (H1N1) than the elderly who often had no fever, and that persons under 60 were susceptible to infection with influenza virus A (H1N1), as indicated by the results of several serological studies^{30, 41–44}.

According to the literature, between 44% and 84% of adult hospitalized patients with seasonal influenza have an underlying disease, and similar results were obtained in the case of patients with novel influenza¹⁵⁻³¹. Perez-Padilla et al.³⁵ showed 18 patients with pneumonia of which 50% had an underlying disease, while the study of Cui et al.¹⁸ recorded an underlying disease in 34% of 68 patients. In the study of Louie et al.²⁶ risk factors for developing complications associated with influenza had 68% of patients, in the study of Lee et al.²⁹ 79%, and in the study of Jain et al.¹⁷ 82% of the patients. In contrast, in our study predisposing diseases for the development of severe forms of influenza had only 21% of the patients, although the number of patients with risk factors was higher when taking into account a pregnant woman, obese patients and smokers. A small number of patients with primary disease may be interpreted by their demographics and the fact that they were members of the army, who are usually healthy young people. In patients with seasonal influenza asthma and COPD are the most common underlying diseases, which coincides with data from some studies on patients with novel influenza¹³⁻²⁰.

The main comorbidities in critically ill patients with influenza A (H1N1) in the United States and Mexico were chronic lung disease, obesity, hypertension, diabetes and smoking cigarettes, while in our study there were mostly cardiovascular diseases and diabetes^{15, 17, 19, 22, 26}. According to the results of some studies obesity, pregnancy and COPD were associated with the development of severe forms of pneumonia caused by influenza A virus (H1N1), often with ARDS, but age, high APACHE II and SOFA scores and deferred antiviral therapy with higher morbidity and mortality¹⁹⁻²⁶.

Physiological changes and immune "deviation" from cell to humoral immunity that occurs during pregnancy are hypothetical preconditions for an increased vulnerability of pregnant women. Pregnant women were at higher risk of morbidity and mortality during novel influenza, similar to the earlier period of seasonal and pandemic influenza³⁹⁻⁵¹. Denholm et al.¹⁴ in their study of 112 cases of influenza A (H1N1), among who were 15 pregnant women, claimed that pregnant women were at high risk of developing severe and fatal form of the disease, which required urgent application of antiviral therapy. The percentage of hospitalizations of pregnant women suffering from novel flu in our study was small, as compared to other studies that ranged up to 10%^{17, 39-51}. Those differences in the number of hospitalized pregnant women between this and other studies can be explained by the fact that the majority of our patients belonged to a group of previously healthy, young male with military health insurance.

According to the available literature data the number of hospitalized obese patients with influenza A (H1N1) was higher than in our group. For example, Jain et al.¹⁷ reported that 45% of hospitalized patients were obese, and half of them extremely obese, while the number of obese in the study of Domínguez-Cherita et al.²² was 36%. Cui et al.¹⁸ took the example of 32% of obese patients in their study and

showed that obesity as a risk factor was associated with higher mortality rate from influenza A (H1N1). Similarly Lee et al.¹⁹ presented a series of 47 fatal cases of influenza A (H1N1), among them 58% of obese patients. Obese patients often have other comorbidities that are associated with increased risk of developing complications of influenza, and even death. For example, one of the deceased patients in our study, in addition to extreme obesity also had hypertension and was a smoker.

Hospitalized patients of seasonal and pandemic influenza A (H1N1) have a similar clinical presentation, whether it is a mild or severe disease²⁷⁻³⁶. However, unlike seasonal influenza, where gastrointestinal symptoms are described mainly in children in less than 5%, in our and other studies in patients with novel flu, gastrointestinal symptoms were more common, both in children and adults. Cui et al.¹⁸ showed that 52% of patients with pneumonia and novel influenza had a reduced number of CD4 + cells and that lymphopenia, which was not improving for five days from the onset of treatment was a factor associated with death. We did not discuss the relationship of certain blood parameters with patient outcome, but we noticed that the number of patients with leukopenia and thrombocytopenia was similar to that of other authors¹⁷.

The most severely ill patients and those who died had the highest values of lactate dehydrogenase and creatine kinase, but their prognostic value was not interpreted²²⁻²⁶. In seasonal influenza, during the peak period up to 90% of the total number of death were registered among persons older than 65, while the highest mortality in patients with novel flu was recorded in the age of 20 to 49 years²⁷⁻³⁶. Increased mortality in younger patients as compared to those over 59 years when it comes to a novel influenza could be explained by the presence of cross protective antibodies to influenza A (H1N1), which can be found in older patients because they were exposed to different strains of A (H1N1) during 1950^{30, 41-44}.

In seasonal influenza, bacterial superinfections are registered in 6-24% of the patients, which are mostly caused by *Staphylococcus aureus*. In previous pandemics of influenza the majority of deaths were associated with bacterial pneumonia. According to the Center for Disease Control 29% of 77 patients who died from novel influenza had bacterial infection, and in 10 of them *Streptococcus pneumoniae* was confirmed^{27-31, 52-55}. Lee et al.¹⁹ described 28% of bacterial superinfections among a series of 47 fatal cases of influenza A (H1N1). Louie et al.²⁶ registered a secondary bacterial infection in only 4% of the patients with novel flu, while we noticed a positive blood culture in three patients treated in the ICU. A small number of bacterial infections in our study was associated with a small number of patients treated in the ICU and the application of antibiotics before obtaining samples for culture.

Novel flu was expressed in a severe form such as pneumonia, ARF and ARDS, in about 1/3 of the patients, which resulted in admission to the ICU of 6% of the patients, similar to the study of Domínguez-Cherita et al.²². In a slightly more than 1/3 of the patients we registered the

risk factors for developing severe forms of influenza, but they did not have a significant impact on the development of pneumonia. This is consistent with the experience of other authors, according to whom a severe form of new influenza primarily affects young and previously healthy people¹⁷⁻¹⁹. One of the conclusions of the Jain et al.¹⁷ was that pandemic strain of influenza virus A (H1N1) causes severe disease accompanied by pneumonia, ARDS and death in a significant number of previously healthy young people. In this prospective study, pneumonia was registered in 40.2% of the patients, usually in the form of bilateral infiltrates (26.5% of patients), whereas in our study, pneumonia occurred in less than 1/3 of patients, usually in the form of unilateral infiltrates. Among hospitalized patients with influenza A (H1N1) presented by Louie et al.²⁶ as many as 66% had pneumonia and 31% were admitted to ICU. Zhao et al.²⁸ presented 68 patients with pneumonia and confirmed influenza A (H1N1), of which 44% were admitted to ICU. Many of these patients had been previously healthy and only few over 65 years.

A number of authors suggested that clinical course of swine flu can be very severe, especially in patients with comorbidities and may be accompanied by high mortality. The experience gained during a pandemic showed that novel influenza can go into ARDS with refractory hypoxemia in healthy young person for a few hours and may result in rapid death. The first publications on patients with severe influenza A (H1N1) and ARDS showed variable mortality of 15%–40%²¹⁻²⁶. That may be due to different populations of patients included in the study, the different characteristics of ARDS, and various human and material resources in the ICU in individual countries. The highest rate of mortality (41.4%) was described in Mexico, the first one to be affected by pandemic influenza²². Davies et al.²⁶ showed 68 cases of new influenza with severe ARDS that were treated with extracorporeal membrane oxygenation with mortality rate of 21%²⁶.

Cui et al.¹⁸ presented 68 patients with confirmed influenza A (H1N1), of which 44% admitted to ICU with a mortality of 14.7%. According to the study of Jain et al.¹⁷ mortality was noted in 28.4% of 67 patients treated in ICU. Denholm et al.¹⁴ pointed out 26.8% of 112 patients with novel influenza admitted to ICU and mortality of 10%. Kumar et al.²³ showed that total mortality among critically ill patients on the day 28 was 14.3%, and on the day 90 17.3%, which was significantly lower than in other studies. In our study, novel flu resulted in death in about 1/3 of the patients admitted to ICU and in only 2% of all hospitalized patients.

Influenza A (H1N1) is almost always sensitive to neuraminidase inhibitors, oseltamivir and zanamivir. In this context, antiviral therapy should be given in all hospitalized patients with influenza A (H1N1), in pregnant and all immunocompromised outpatients⁵⁵⁻⁶². The study of Belongia et al.¹⁵ published in 2010 in favor of these views and suggested that the risk of serious complications of influenza A (H1N1) was not greater than the risk for recent seasonal influenza. There is a consensus on the highest benefit of antiviral therapy if the treatment starts early, in the first 48 hours after the

onset of novel influenza. However, antiviral drugs should not be withheld in any other patient in whom it has been more than 48 hours after the onset of a novel flu⁵⁶⁻⁶¹. Prospective studies, in which the oseltamivir therapy was conducted in hospitalized patients with influenza, showed a significant reduction in mortality, even when the treatment started within 48 hours after the onset^{61,62}.

The results of the majority of previous studies indicate that delayed antiviral therapy may have impact on the increased severity of disease and mortality in patients with influenza A (H1N1). Lee et al.¹⁹ showed that the time from the onset of influenza A (H1N1) to the hospitalization was longer for non-survivors than for survivors (3 vs 2 days, $p < 0.05$), like the time for beginning oseltamivir therapy (6.5 vs 3 days, $p < 0.01$). The patients with fatal outcome in this study rarely received oseltamivir in the first two days of hospitalization in contrasts to survivors (61% vs 96%, $p < 0.01$). The results of our study also suggest that antiviral therapy in patients with novel flu could be useful, especially when started early in the disease. We administered oseltamivir in 68.4% of the patients, of whom nearly 43% received the drug in the first 48 hours after the onset of the illness. The appearance of ARDS in the patients who received oseltamivir in the first 48 hours from the onset of the illness was three times higher as compared to those who received the therapy after 48 hours. However, the number of patients with ARDS in our country was small to make a reliable conclusions. Jain et al.¹⁷ applied antiviral therapy in 75% of hospitalized patients after the average time from the beginning of flu and the therapy of 3 days (0–29 days). However, in the first 48 hours of the onset of novel influenza antiviral therapy was applied an only 39% of patients. Patients admitted to ICU and those with fatal outcome, compared to patients with less severe form of flu rarely received antiviral therapy during the first 48 hours after the onset of stroke (23% vs 86%). The average time from the start of flu to the introduction of antiviral therapy in the deceased patients was 8 days (3–20 days), in patients admitted to the ICU 6 days (0–24 days), which is longer than in our study¹⁷. We prescribed oseltamivir in almost all of the patients immediately after the reception, which might be attributed to the small number of admission to the ICU in our study. In the study of Louie et al.²⁶ mortality was 10.8%, although 79% of patients received antiviral therapy. The most common cause of death in this study was viral pneumonia and ARDS²⁶. These results can probably be caused by a delayed antiviral therapy.

Some studies showed that bacterial pneumonia was associated with influenza A (H1N1) in 30% of cases admitted to the ICU, which required early antibiotic therapy in combination with antiviral therapy⁵². In this regard, in most studies, including our, antibiotic therapy was administered in almost all hospitalized patients¹⁷. For example, Jain et al.¹⁷ applied antiviral therapy in 73% and antibiotic therapy in 97% of patients with pneumonia. In this study, all patients with lethal outcome were treated with antibiotics, while antiviral therapy received 90% of the patients. According to some authors the use of antibiotics in patients

with influenza A (H1N1) and pneumonia is necessary because of the lack of reliable diagnostic methods for bacterial pneumonia^{17, 30–32}. However, this view is difficult to support, taking into account the availability of high quality and rapid laboratory-microbiological analysis (C-reactive protein, procalcitonin, detection of bacterial antigens, etc.). However, we also applied antibiotic therapy in 90% of the patients with influenza A (H1N1) and in all of those with pneumonia.

Conclusion

Pandemic influenza A (H1N1) is mainly manifested as a mild acute respiratory disease, which usually affects young adults. A small number of patients develop severe forms of the disease and the development of ARDS occurs more frequently in patients with risk factors. Application of oseltamivir can be very useful, especially when treatment is started within the first 48 hours after onset.

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