® Postepy Hig Med Dosw (online), 2013; 67: 595-600
e-ISSN 1732-2693

www.phmd.pl
Original Article

Received: 2013.01.07
Accepted: 2013.05.15
Published: 2013.06.20

The Clinical Course of Late Diagnosed Fatal Cases of A (H1N1) Influenza in Poland

Przebieg kliniczny późno rozpoznanych śmiertelnych przypadków grypy A (H1N1) w Polsce

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Marta Rorat[1,2, A, B, D, E, F], **Tomasz Jurek**[1, A, D], **Ernest Kuchar**[2, D, F], **Leszek Szenborn**[2, D]

[1] Department of Forensic Medicine, Wroclaw Medical University, Poland
[2] Department of Paediatrics and Infectious Diseases, Wroclaw Medical University, Poland

Summary

Introduction: The most frequent complication of A (H1N1) influenza and the leading cause of death was pneumonia with a primary viral or mixed viral and bacterial etiology. 182 patients had died because of a pandemic influenza in Poland by 31st July 2010.

Material and Methods: A retrospective study of 6 fatal cases of pandemic influenza, aged 23-41, including 3 women, hospitalised between November 2009 and February 2011 in different Polish medical centres.

Results: We present the clinical course of 6 late diagnosed cases of A (H1N1) influenza. All patients presented typical flu-like symptoms in the beginning. 4/6 patients had severe disease risk factors: pregnancy, arthritis, Wegener granulomatosis and obesity. All patients were seen by doctors, no one had received antiviral therapy, 4/5 were treated with antibiotics before they were hospitalized. One patient had nosocomial infection. Patients were admitted to the hospital on the 3rd to 8th day of the disease. They received oseltamivir treatment on the 4th to 9th day. All patients developed pneumonia complicated by acute respiratory distress syndrome. Death appeared between the 4th and 27th day after the onset of symptoms. Autopsies were performed in 5 cases and revealed haemorrhagic pneumonia in 2 patients.

Conclusion: Delayed diagnosis and antiviral treatment initiation has a significant impact on mortality in A (H1N1) influenza. During the influenza epidemic, patients presenting typical symptoms should always be suspected of having influenza. Antiviral treatment has to be initiated immediately, especially if there are risk factors of severe disease.

Keywords: swine influenza • pneumonia • pandemic • delayed diagnosis • antiviral agents

Full-text PDF: http://www.phmd.pl/fulltxt.php?ICID=1053910

Word count: 2679
Tables: 2
Figures: –
References: 25

Author's address: Marta Rorat, M.D. Department of Forensic Medicine, Wroclaw Medical University, Mikulicza Radeckiego 4, 50-368 Wroclaw, Poland; e-mail: rorat.marta@gmail.com

Introduction

In April 2009, in Mexico, there was an outbreak of a new A (H1N1) influenza virus [5]. The virus spread rapidly worldwide. The highest level of an influenza pandemic was announced by the WHO on 11th June 2009 [23]. Spain was the first European country with a laboratory to confirm a H1N1 influenza pandemic [18]. Mortality in H1N1 cases was similar to that of seasonal influenza [3,20]. The first case in Poland was documented on 6th May 2009. The highest incidence of H1N1 influenza occurred in November and December 2009. A total of 182 patients had died because of A (H1N1) influenza by 31st July 2010 [4]. As some studies showed, pandemic influenza was different to the seasonal one. It mainly concerned relatively young people (under the age of 60), who were relatively healthy beforehand. As with seasonal influenza, people with underlying health conditions and pregnant women were in the group with an increased risk of a severe disease. Obesity and delayed antiviral treatment have been identified as major risk factors of a severe outcome and higher mortality [6,7,11,14,16,19,20,22]. The most frequent complication in H1N1 influenza was pneumonia with a primary viral or mixed viral and bacterial aetiology (especially *Streptococcus pneumoniae* and *Staphylococcus aureus*) [7,13,14,22]. Death usually occurred as a result of acute respiratory distress syndrome (ARDS) [7,14,17]. During the influenza H1N1 pandemic, due to the infection's prophylaxis limitations, the crucial tasks were prompt diagnosis, assessing the risk of severe disease and the immediate initiation of adequate antiviral therapy.

Material and Method

A retrospective analysis of six fatal cases during the A (H1N1) influenza pandemic of patients hospitalised between November 2009 and February 2011 in different Polish medical centres was performed. All patients were confirmed with 2009 H1N1 influenza by rRT-PCR – using pharyngeal or nasopharyngeal swabs. The study protocol included the following information: age, sex, comorbid conditions, contact with people with acute respiratory infection, the time from the onset of symptoms to the first visit to the doctor, number of visits to the doctors until hospitalisation, the time from the onset of symptoms until hospitalisation, the time from hospital admission to ICU admission, the time spent in hospital, the time from the onset of symptoms to death, and the time from the onset of symptoms to the initiation of antiviral therapy. The study protocol comprised data included in medical records as well as testimony provided by medical staff and patients' family members during court proceedings on the alleged malpractice. Obesity was defined as a BMI ≥30. We recorded the clinical course – signs, symptoms, selected laboratory results, blood gas analysis, radiological findings and the history of treatment.

Results

Clinical characteristics

We describe 6 fatal cases of 2009 H1N1 influenza, treated in 6 different Polish hospitals from November 2009 to February 2010. The age of the patients ranged from 23 to 41 years. There were 3 males and 3 females. Four patients had underlying conditions – one had unidentified chronic arthritis treated with methylprednisolone, one was newly diagnosed with Wegener granulomatosis treated with methylprednisolone and cyclophosphamide, one was pregnant (31 weeks) and one was extremely obese (BMI 40). The others did not have any identifiable risk factors of any severe disease. Four patients had family contact with people who had a flu-like illness (H1N1 not confirmed). One patient with Wegener granulomatosis was infected during hospitalisation in the

Table 1. Symptoms observed in patients with A (H1N1) influenza before hospitalization

Symptoms	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Fever						
38-39°C	+	+	+		+	
39.1-40°C				+		+
Cough	+	+	+	+	+	+
Sore throat	+	+		+	+	
Haemoptysis	+	+				
Rhinorrhoea	+					
Fatigue	+	+	+	+	+	+
Myalgia/arthralgia	+	+		+	+	
Nausea, vomiting	+			+		
Diarrhoea	+					+
Headache				+		
Chest pain	+					

Table 2. Diagnostic findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Leukocyte count < 4 x 10^3/µl 4-10 x 10^3/µl > 10 x 10^3/µl	+	+	+	+	+	+
Lymphopenia <1.5 x 10^3/µl	+	+	-	+	+	+
Anaemia Hb<12g/dl	-	-	-	-	+ (during pregnancy)	+
Thrombocytopenia <150 x 10^3/µl	-	-	+	-	+	+
CRP mg/dl	No data	16.63-23.28	50	422	75.1-221.03	>90
AspAT	No data	81-1868	75	-	Normal	Normal
AlAT	No data	74-718	58	-	Normal	Normal
Creatinine	No data	Normal	Normal	-	Normal	Haemodialysis
Rapid test H1N1 influenza	Not made	Negative	Not made	Negative	Not made	Not made
Chest X-ray	Inflammatory changes	Inflammatory changes	Inflammatory changes	Inflammatory changes	Inflammatory changes	Inflammatory changes, cardiomegaly

internal medicine and nephrology department; therefore, the study protocol does not fully apply to this case. None of the patients had been vaccinated against pandemic H1N1 influenza. The duration of symptoms before the first visit to the doctor ranged from 1 to 4 days. The duration of symptoms before hospitalisation ranged from 3 to 8 days. None of the patients received antiviral treatment before admission to hospital, though all of them sought medical help several times (ranging from 3 to 5 times). All patients had a fever over 38°C, a cough and fatigue before admission to hospital – 4 complained of a sore throat and myalgia/arthralgia, 2 complained of nausea/vomiting, 2 had diarrhoea (Table 1).

The other symptoms were rhinorrhoea, haemoptysis, headache and chest pain. The patients were diagnosed with pharyngitis, tracheitis, bronchitis, viral infection, respiratory infection and in one case seasonal influenza. The first symptoms of influenza in the patient with Wegener granulomatosis were fever, fatigue and diarrhoea. After 2 days, the cough and dyspnoea appeared. In 5 cases, the main cause for visiting the hospital was lack of improvement in the physical condition or intensification of symptoms despite the treatment. Upon admission, 3 patients had dyspnoea and 2 had auscultatory phenomena. During hospitalisation, all the patients developed respiratory failure and required intensive care. The time from hospital admission to ICU transfer was < 12 h in 3 out of 5 cases. Consequently, the interval between the onset of symptoms and ICU admission ranged from 6 to 9 days. The patient with Wegener granulomatosis required mechanical ventilation after 3 days of symptoms. He was also haemodialysed because of kidney failure, which appeared during the course of the underlying disease (before the influenza).

Diagnostics

In all patients, at the time of hospital admission, we found abnormalities in their blood morphology (Table 2). 4/5 patients had lymphopenia with normal total white blood counts and 2/5 had thrombocytopenia. The patient with Wegener granulomatosis had pancytopenia because of his underlying disease. C-reactive protein concentration was elevated in all cases, but in one case it was extremely high (422 mg/dl). Slightly increased liver transaminase activity (GOT – glutamic oxaloacetic transaminase; and GPT – glutamic pyruvic transaminase) was found in 2 patients – one was extremely obese and developed liver failure during hospitalisation. In all cases, blood gas analyses proved hypoxemia, which persisted regardless of oxygen therapy. All patients had chest X-rays on the day of hospital admission and they all had bilateral infiltrates indicating pneumonia.

All patients were tested for A (H1N1) influenza using real time PCR. In 2 cases, a rapid influenza test was performed – the results were negative. Microbiology diagnostics revealed bacterial superinfection in 2 cases. In the first patient, *Staphylococcus aureus* MLSB (+) was isolated from the sputum. In the second (the patient with Wegener granulomatosis), *Acinetobacter baumannii* sensitive to cefoperazone and colistin was isolated from the blood. The patient with Wegener granulomatosis also had CMV reactivation (CMV DNA in the blood).

Treatment

Four patients were treated with antibiotics before admission to hospital. One person received one type and 3 patients received two types of antibiotics. The most commonly used antibiotic was cefuroxime, which was administered in 3 cases. The other antibiotics were doxycycline, amoxicillin, azithromycin and gentamicin. In all cases, the antibiotic therapy was changed or initiated after hospital admission. Three patients received cefuroxime (in one case cefuroxime plus amikacin), 3 received amoxicillin with clavulanic acid – in one case ciprofloxacin and in another erythromycin was added. All patients also received oseltamivir. The time from the onset of the illness to the initiation of oseltamivir therapy was 7-9 days. None of the patients were given the test for the resistance of the H1N1 influenza virus to oseltamivir. The patient with Wegener granulomatosis was initially treated with amoxicillin with clavulanic acid and ciprofloxacin. After two days cefuroxime was added, which was changed to another antibiotic – imipenem. The time from the onset of illness to the initiation of oseltamivir therapy was 4 days. All patients were treated in the ICU because of respiratory distress. They all required mechanical ventilation. In the pregnant woman, because of impaired oxygenation, a caesarean section was performed. In this case, high frequency oscillatory ventilation and ventilation in the supine position were also used. Interventions such as ECMO or extracorporeal CO_2 removal were not used in any case.

Death

Death appeared between the 4^{th} and 27^{th} day after the onset of symptoms – later in patients without severe course risk factors. All patients developed acute respiratory distress syndrome (ARDS). The final cause of death in 4 patients was cardiorespiratory failure. In 2 patients it was multi-organ dysfunction syndrome. Autopsies were performed in 5 cases, all by a pathologist. The post-mortem examination was not performed in the patient with Wegener granulomatosis. In all cases the autopsy revealed features of pneumonia. In two cases haemorrhagic pneumonia was found (in one of them an image of purulent pneumonia), in two others lung fibrosis. In the obese patient and the pregnant woman, liver steatosis was also diagnosed.

Discussion

We have presented six fatal cases of pandemic (H1N1) influenza relating to patients who were hospitalised in Poland between November 2009 and February 2010. All patients developed pneumonia and consequently ARDS, and they required treatment in the ICU. All our patients were young – age ranged from 23 to 41 years. As many studies have shown, the H1N1 influenza virus mostly infected people between 60 and 65 years old [6,7,11,14,17,19,20,22,25].

In our study, 4 patients had risk factors of severe diseases: chronic arthritis, Wegener granulomatosis, pregnancy and obesity. Despite many disturbing reports on the dramatic increase in the number of overweight/obese people (obesity epidemic) and the health consequences of this condition [8,15], excessive body weight is still commonly perceived as a physiological status – a variant of the norm. People rarely recognize the correlation between obesity and the prevalence of chronic, more infectious diseases. In pandemic influenza cases, excessive body weight has proved to be a very important risk factor of severe illness, associated with higher mortality [6,7,11,20,22]. For example in the Cui et al. [6] study 32% and in the Viasus et al. [22] study 28% of hospitalised patients were obese.

The next risk factor was pregnancy. The studies showed that the mortality in the severe course of H1N1 influenza in pregnant women was up to 20% [19,20,22,25]. High risk of influenza with a poor outcome during pregnancy was associated with respiratory, cardiac and immune system changes [9]. It was higher in women with chronic diseases, especially with asthma and obesity. Complications occurred more often in the second and third trimester of pregnancy and in multigravida patients [11,16,25]. During the pandemic, the rate of premature birth also increased – 30.2% in the Siston et al. [16] study and 57.8% in the Zhang et al. [25] study. This was clearly associated with a higher rate of neonatal death [16,25].

In our study, two patients had pre-existing medical conditions, which predispose to a poor outcome. In one case, it was chronic arthritis which appeared in the course of the undetermined systemic disease. The woman was treated with steroids for several months. Based on the medical records, the authors established that the patient was not treated regularly and her ailments, in the period preceding the A (H1N1) infection, were exacerbated. The second patient was immunocompromised because of Wegener granulomatosis. Many authors have presented the relation between the severity of the influenza, the higher death rate and pre-existing medical conditions. Besides obesity, the most common underlying medical conditions were asthma, chronic obstructive pulmonary disease, diabetes, cardiac and liver diseases, neoplasms, renal failure and immunosuppression [6,7,11,14,17,19,22]. Tabarasi et al. [19] also highlighted drug abuse.

The other important risk factor which influenced the mortality rate during the pandemic was bacterial co-infection. The most common identified strains were *Streptococcus pneumoniae* and *Staphylococcus aureus* [7,11,13,22]. In our study, one patient had pneumonia caused by a coexisting H1N1 virus and *Staphylococcus aureus*. In the patient with Wegener granulomatosis, *Acinetobacter baumannii* was isolated from the blood. Because of immunosuppressive treatment, he also had CMV reactivation. Viasus et al. [22] showed that early treatment with oseltamivir was associated with less evidence of pneumonia and bacterial co-infections.

In our data, the clinical features of influenza included fever, cough, fatigue, sore throat, myalgia or arthralgia, nausea/vomiting, diarrhoea, rhinorrhoea, haemoptysis, headache and chest pain. These symptoms have also been reported in many other studies [6,7]. The laboratory tests performed upon admission showed lymphopenia and thrombocytopenia and the CRP level was elevated in each case. Many authors have reported the association between increased CRP concentration or lymphopenia and severe illness [14].

In our study group, the H1N1 2009 influenza infection was confirmed by an rRT-PCR assay. Only 2 patients had a rapid test for H1N1 influenza and in both cases the result was negative. In these cases it was the reason for a one-day delay in treatment. A number of studies have proven the rapid tests to have too low sensitivity. Thus, further proceedings should not be dependent on their negative results [11,21]. The rRT-PCR is the most sensitive and specific influenza diagnostic test but false negatives can also occur. According to the CDC the sensitivity in an rRT-PCR assay is 86-100% [1].

During the pandemic, the CDC recommended introducing early empiric antiviral therapy with oseltamivir in patients with flu-like symptoms without undue delay (without waiting for the test result or the symptoms of severe disease), especially in patients who were at increased risk of complications from influenza [2]. The therapy was most effective if it was initiated within 48 hours from the onset of symptoms [2,24]. Despite this, there were studies that provided evidence that treatment with oseltamivir in patients admitted to hospital even after 48 hours may reduce mortality [11,12,24]. Late initiation of therapy was clearly associated with a higher risk of severe illness and mortality [16,19,22]. In all our cases, the initiation of treatment was significantly delayed. It was caused by the fact that the doctors, despite the typical flu-like symptoms, did not suspect a H1N1 infection at the very beginning of the illness. The diagnosis of pandemic influenza was only made during hospitalisation. Polish recommendations for the management of patients suspected of having H1N1 influenza were not precise [10]. As a result, many doctors did not know how to deal with such patients.

None of our patients were vaccinated. In Poland, due to the Minister of Health's decision, a vaccine against H1N1 influenza was not available, even for healthcare workers. Therefore, preventive options were limited. The therapeutic options in patients with severe disease (hospitalised in the ICU) were also limited. Unconventional therapies such as ECMO, high frequency oscillatory ventilation or extracorporeal CO_2 removal were only available in a few hospitals in the country, access to these centres was limited and experience in the use of these therapies in influenza cases was poor.

We excluded one case of a pregnant woman (22 weeks) from the report. The patient was admitted to the hospital in December 2009 with influenza-like symptoms: fever up to 40°C, sore throat, cough, fatigue, myalgia and arthralgia, and dyspnoea, and also complaints about dysuric symptoms. The disease lasted 2 days. Upon admission, the patient had peripheral cyanosis and disturbances in blood gas analyses (hypoxemia and acidosis). She also had a urinary tract infection. She was treated with oseltamivir (from the first day of hospitalisation) and antibiotics. In this case both the rapid test and PCR were negative. Her condition deteriorated in a couple of days; she developed ARDS and required intensive care with mechanical ventilation in the ICU. During transportation to the other department, she had a cardiac arrest. The ultrasound performed during the resuscitation revealed a rupture of the spleen (perhaps after cardiac massage). She died five days after the onset of symptoms. The autopsy revealed haemorrhagic pneumonia and features of pyelonephritis.

Our study has some limitations. First of all, it refers to a small number of cases. The group is heterogeneous and the patient selection was random. The other issue is the limited material in the histopathological reports. They only include basic information and lack important details. The reports were prepared by a few different pathologists. The patients were treated in different hospitals and did not have the same diagnostics, so not all information required was collected. Nevertheless, this is a good illustration of problems experienced in Poland during the A (H1N1) influenza pandemic.

Conclusions

Delayed diagnosis and antiviral treatment initiation has a significant impact on mortality in A (H1N1) influenza. During the influenza epidemic, patients presenting typical symptoms should always be suspected of having influenza. Antiviral treatment has to be initiated immediately, especially if there are risk factors of severe disease. Diagnostic and therapeutic procedures should concentrate on respiratory sufficiency as pneumonia (viral and secondary bacterial) is a major cause of death.

References

[1] CDC Health Alert Network (HAN) info service message. Interim recommendations for clinical use of influenza diagnostic tests during the 2009-10 influenza season. September 29, 2009. Available at: http://www.cdc.gov/h1n1flu/guidance/diagnostic_tests.htm (20.07.2012)

[2] CDC Health Alert Network (HAN) info service message. Recommendations for early empiric antiviral treatment in persons with suspected influenza who are at increased risk of developing severe disease. October 19, 2009. Available at: http://www.cdc.gov/H1N1flu/HAN/101909.htm (20.07.2012)

[3] Chang Y.S., van Hal S.J., Spencer P.M., Gosbell I.B., Collett P.W.: Comparison of adult patients hospitalised with pandemic (H1N1) 2009 influenza and seasonal influenza during the "PROTECT" phase of the pandemic response. Med. J. Aust., 2010; 192: 90-93

[4] Chief Sanitary Inspector. The report on influenza epidemiologic status in Poland. 2010. Available at: http://www.pis.gov.pl/userfiles/file/Departament%20Przeciwepidemiczny/grypa%20H1N1/KomunikatGrypa2331072010.pdf (03.07.2012)

[5] Chowell G., Bertozzi S.M., Colchero M.A., Lopez-Gatell H., Alpuche-Aranda C., Hernandez M., Miller M.A.: Severe respiratory disease concurrent with the circulation of H1N1 influenza. N. Engl. J. Med., 2009; 361: 674-679

[6] Cui W., Zhao H., Lu X., Wen Y., Zhou Y., Deng B., Wang Y., Wang W., Kang J., Liu P.: Factors associated with death in hospitalised pneumonia patients with 2009 H1N1 influenza in Shenyang, China. BMC Infect. Dis., 2010; 10: 145

[7] Gill J.R., Sheng Z.M., Ely S.F., Guinee D.G., Beasley M.B., Suh J., Deshpande C., Mollura D.J., Morens D.M., Bray M., Travis W.D., Taubenberger J.K.: Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Arch. Pathol. Lab. Med., 2010; 134: 235-243

[8] Guh D.P., Zhang W., Bansback N., Amarsi Z., Birmingham C.L., Anis A.H.: The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health, 2009; 9: 88

[9] Jamieson D.J., Theiler R.N., Rasmussen S.A.: Emerging infections and pregnancy. Emerg. Infect. Dis., 2006; 12: 1638-1643

[10] Kopacz E.: Minister of Health. The change in rules of conduct with patients visiting doctors with flu-like symptoms. Warsaw, 3rd August 2009. Available at: http://www.gis.gov.pl/?news=175 (05.07.2012)

[11] Louie J.K., Acosta M., Winter K., Jean C., Gavali S., Schechter R., Vugia D., Harriman K., Matyas B., Glaser C.A., Samuel M.C., Rosenberg J., Talarico J., Hatch D.: Factors associated with death or hospitalisation due to pandemic 2009 influenza A (H1N1) infection in California. JAMA, 2009; 302: 1896-1902

[12] McGeer A., Green K.A., Plevneshi A., Shigayeva A., Siddiqi N., Raboud J., Low D.E., Toronto Invasive Bacterial Diseases Network: Antiviral therapy and outcomes of influenza requiring hospitalisation in Ontario, Canada. Clin. Infect. Dis., 2007; 45: 1568-1575

[13] Palacios G., Hornig M., Cisterna D., Savji N., Bussetti A.V., Kapoor V., Hui J., Tokarz R., Briese T., Baumeister E., Lipkin W.I.: Streptococcus pneumonia coinfection is correlated with the severity of H1N1 pandemic influenza. PLoS One, 2009; 4: e8540

[14] Reyes S., Montull B., Martínez R., Córdoba J., Molina J.M., Martí V., Martínez A., Ramírez P., Menéndez R.: Risk factors of A/H1N1 etiology in pneumonia and its impact on mortality. Respir. Med., 2011; 105: 1404-1411

[15] Selassie M., Sinha A.C.: The epidemiology and etiology of obesity: a global challenge. Best Pract. Res. Clin. Anaesthesiol., 2011; 25: 1-9

[16] Siston A.M., Rasmussen S.A., Honein M.A., Fry A.M., Seib K., Callaghan W.M., Louie J., Doyle T.J., Crockett M., Lynfield R., Moore Z., Wiedeman C., Anand M., Tabony L., Nielsen C.F. et al.: Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. JAMA, 2010; 303: 1517-1525

[17] Soto-Abraham M.V., Soriano-Rosas J., Díaz-Quiñónez A., Silva--Pereyra J., Vazquez-Hernandez P., Torres-López O., Roldán A., Cruz--Gordillo A., Alonso-Viveros P., Navarro-Reynoso F.: Pathological changes associated with the 2009 H1N1 virus. N. Engl. J. Med., 2009; 361: 2001-2003

[18] Surveillance Group For New Influenza A (H1N1) Virus Investigation and Control in Spain: New influenza A (H1N1) virus infections in Spain, April-May 2009. Euro Surveill., 2009; 14:19. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19209 (20.05.2013)

[19] Tabarsi P., Moradi A., Marjani M., Baghaei P., Hashemian S.M., Nadji S.A., Fakharian A., Mansouri D., Masjedi M., Velayati A.: Factors associated with death or intensive care unit admission due to pandemic 2009 influenza A (H1N1) infection. Ann. Thorac. Med., 2011; 6: 91-95

[20] Vaillant L., La Ruche G., Tarantola A., Barboza P.: Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. Euro Surveill., 2009; 14: 33

[21] Vasoo S., Stevens J., Singh K.: Rapid influenza antigen test for diagnosis of pandemic (swine) influenza A/H1N1. Clin. Infect. Dis., 2009; 49: 1090-1093

[22] Viasus D., Pano-Pardo J.R., Pachon J., Campins A., Lopez-Medrano F., Villoslada A., Fariñas M.C., Moreno A., Rodríguez-Baño J., Oteo J.A., Martínez-Montauti J., Torre-Cisneros J., Segura F., Gudiol F., Carratalà J.: Factors associated with severe disease in hospitalized adults with pandemic (H1N1) 2009 in Spain. Clin. Microbiol. Infect., 2011; 17: 738-746

[23] World Health Organization. Pandemic (H1N1) 2009. Available at: http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html (17.05.2013)

[24] Yang S.G., Cao B., Liang L.R., Li X.L., Xiao Y.H., Cao Z.X., Jia H.Y., Yu H.J., Xu Z., Gu L., Yang Y.D., Chen Y., Du W.B., Yan X.X., Liang Z.A.. et al.: Antiviral therapy and outcomes of patients with pneumonia caused by the influenza A pandemic (H1N1) virus. PLoS One, 2012; 7: e29652

[25] Zhang P.J., Li X.L., Cao B., Yang S.G., Liang L.R,.Gu L., Xu Z., Hu K., Zhang H.Y., Yan X.X., Huang W.B., Chen W., Zhang J.X., Li L.J., Wang C. National Influenza A Pandemic (H1N1) 2009 Clinical Investigation Group of China: Clinical features and risk factors for severe and critical pregnant women with 2009 pandemic H1N1 influenza infection in China. BMC Infect. Dis., 2012; 12: 29

The authors have no potential conflicts of interest to declare.