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AVAILABLE TREATMENT APPROACHES OF ACUTE INFLUENZA H1N1 INFECTION AND ITS CLINICAL COMPLICATIONS

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Human H1N1 pandemic developed from the originally localized Mexican source early in the spring 2009. It seems that the current wave of infections slowly moves towards the southern hemisphere; however, the WHO reports on certain foci in Southeast Asia, Western Africa and tropic islands of the Middle America do not exclude another reccurrence in the northern hemisphere. This drew the attention of epidemiologists due to the fact that the virus owns very unique capsid which expresses proteins coded by genes originating from the human, swine and avian influenza virus and was not covered by the available seasonal vaccines. Although most of the cases exibit classical clinical presentation of influenza infection, there are special features like significant gastrointestinal symptomatology and vulnerability of the young population. With respectively small but significant portion of patients there have been noticed fulminant course of infection with poor prognosis including sudden development of respiratory failure and consciousness disturbances which require intensive care unit admission. Cytokine storm should be mentioned as one of the key pathogenic events contributing to the overall mortality in substantial portion of patients. If active immunization is assumed to be preventive measure of proven efficacy, clinicians are still in doubt how to treat a complicated course of infection. We should be aware that the first choice essential drugs, for which viral sensitivity has been certainly proved, are neuraminidasis inhibitors. Here we have to distinct between more available oseltamivir and less available zanamivir and peramivir which until now have shown absolute effectiveness in inhibiting viral strains replication in vivo. Success of direct antiviral protocols has also been noticed with inhaled synthetic nucleoside ribavirine applied locally. Bacterial pneumonia superimposed by the overall patient status should be treated in accordance with the available evidence-based guidelines. We should be aware that septic lung infection caused by multiresistant organisms irrespective of intensive treatment remains the main cause of lethal outcomes in serious clinical presentations of H1N1 infection. *Acta Medica Medianae 2010;49(3):76-82.*

***Ključne reči**: influenza H1N1, treatment, antiviral drugs, pandemic*

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Current pandemic event and virological characteristics of H1N1 strain

One of the outmost pandemic events during last four decades is the present H1N1 influenza occurence. The very first cases of infection were reported somewhere in between the US and Mexico in April, 2009. It seems that the current wave of infections slowly moves towards the southern hemisphere; however, the WHO reports on certain foci in Southeast Asia, Western Africa and tropic islands of the Middle America do not exclude another reccurrence in the northern hemisphere. Although most of the cases exibit classical clinical presentation of influenza infection, there are special features like significant gastro-intestinal simptomatology so unspecific of classical seasonal influenza (1). Vulnerability of young population makes the basic difficulty, and compli-cations are more frequent than we commonly expect. The most efficient tool against this infection is certainly the vaccinination; also, the treatment of already infected patients having complications

remains a huge problem in practise. The number of infected persons rapidly increased last year. Until April 12, 2009 almost 180.000 cases were reported to WHO. Sustainability of interhuman transmission forced WHO to declare the level 6 world pandemic (2). The main Influenza A viral pandemic waves in the past occurred during 1918 -1919 (A/H1N1), 1957-1963 (A/H2N2) and 1968-1970 (A/H3N2).

Influenza A virus is capable of infecting different animal species including birds, pigs and humans. One of the crucial microbiological features of the virus is its impressive genetic instability, and it is assumed to be the cause of huge epidemics. Unlike Influenza B and C, Influenza A virus owns very rare ability to assert genes from both humans and animals.

Influenza A H1N1 viral strain was first isolated in swine tissue samples in 1930, and in humans during 1933. According to its surface antigens, it looked very similar to the influenza A viral strain which was isolated in 1918 (1). In the course of the years to come there has happened recombination and reassortment of different Influenza viral strains of human, swine and avian origin and this lasting process finally led to the creation of Influenza A H1N1 S-OIV subtype. The new S-OIV A (H1N1) virus containes gene combination unseen neither in pig nor human influenza viruses. PB2 and PA genes originating from avian influenza seem to be introduced into the swine strain during 1998 season. PB1 gene out of human H3N2 virus has acquired genes from avian one in 1968. HA, NP and NS genes outsourced from classical swine virus and the remaining two NA and M took roots in the Euroasian swine adapted viral strain (1).

The most significant antigenes are certainly Hemagglutinin and Neuraminidasis, H and N antigens. Any change in these ones leads to the change in viral behaviour and life cycle. Hemagglutinin is a surface protein which is responsible for viral attachment to the carbohydrate receptors on target eucariotic cells and it stimulates the fusion with the cell membrane. This antigene is a common part of any influenza vaccine. Comparing aminoacid sequences of H1N1 from 2009 and the same one isolated in 2008 the expertes from one US military hospital came to conclusion that differences account for even 27,2%. In addition, it is neither similar to the famous 1918 influenza virus (difference accounts for 18%) nor swine influenza from 1976 (12% different) (3). This could be considered hard evidence how often A viral strains really do mutate.

Another external protein is neuraminidasis which serves to provide more secure adhering to the vulnerable cells. It degradates sialic acid surface receptors and provides quicker spreading down the respiratory tract. Antivirals oseltamivir, peramivir and zanamivir act as neuraminidasis inhibitors. If N1 virus gene assortment from 2009 had been similar if not the same as N1 2008 viral strain, assuming possible H1 antigenic differences, we could have expected that 2008 vaccine would be efficient against 2009 strain due to cross reactivity. Unfortunately, it was confirmed that there were substantial N1 antigene differences (18,2%) compared to the 2009 strain (3). Conclusive remarks would be that any vaccine made up for former influenza epidemic lacks cross reactivity with new viral strains, so that the new one must be made, containing current seasonal antigenes.

Clinical presentations of H1N1 infection

Persons considered to be the most vulnerable are children less than 5 years of age, adolescents and young adults, some of them receiving long – term aspirine treatment, pregnant women, patients with chronic diseases - among most common being asthma, cardiovascular, renal and hepatic failure, brain disorders, hematologic, and metabolic disorders, immunosuppresed patients and health workers exposed to the influenza pandemic. These are assumed to be the main risk factors for severe infection (1).

According to its clinical presentation and expected prognosis, we can classify the disease in mild, moderate and severe stages. The mild form exibits fever, cough, sore throat, headache but not dispnea (4).

Moderate clinical presentation has rapid progression of most of the symptoms, and it is followed by dispnea, tachypnea and cough. Chest x-ray can show interstitial pulmonary infiltrates indicating bronchopneumonia. In addition, dehydration is very common due to recurrent vomitting and diarrhoea. Patients with chronic comorbidities can develop exacerbations of asthma, heart and vascular disorders or renal or hepatic insufficiency. These clinical signs require urgent hospital admission (4).

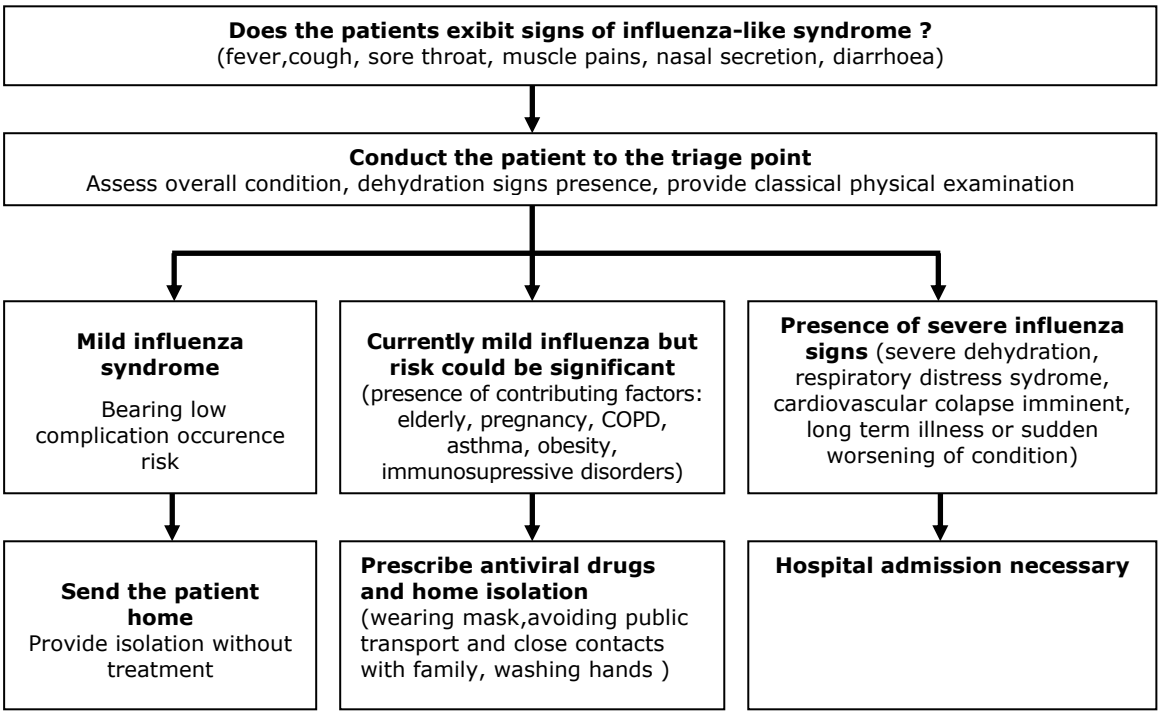
Severe form of disease involves disturbed overall physical condition, dispnea, sometimes apnea, pain in the chest, productive cough with bloody sputum. There are some symptoms indicating brain damage like convulsions or disturbed consciousness. Most patients in this stage of developed infection require assisted ventilation (4).

Dealing with suspected or confirmed H1N1 infection cases at different levels of care

We can easily notice that there are developed and from WHO and CDC recommended procedures in handling the diseased. In that sense from historical military sanitary doctrine it is well known that epidemiological surveilance and proper organisation on the field are much more important for raising survival rates than experienced physicians or quality of equipment available. Therefore, in accordance with this we present an algorythm on handling infected persons in primary care setting.

Recommended procedure differs significantly at secondary and terciary levels of care and assumes selection and follow up of patients in line with natural course of disease and response to treatment. In order to more easily find the assistance on clinical decision making we gave the next algorythm No 2.

Algorythm 1. Outpatient dealing with susceptible / proved H1N1 infection



Algorythm 2. Inpatient treatment of H1N1 infected patients

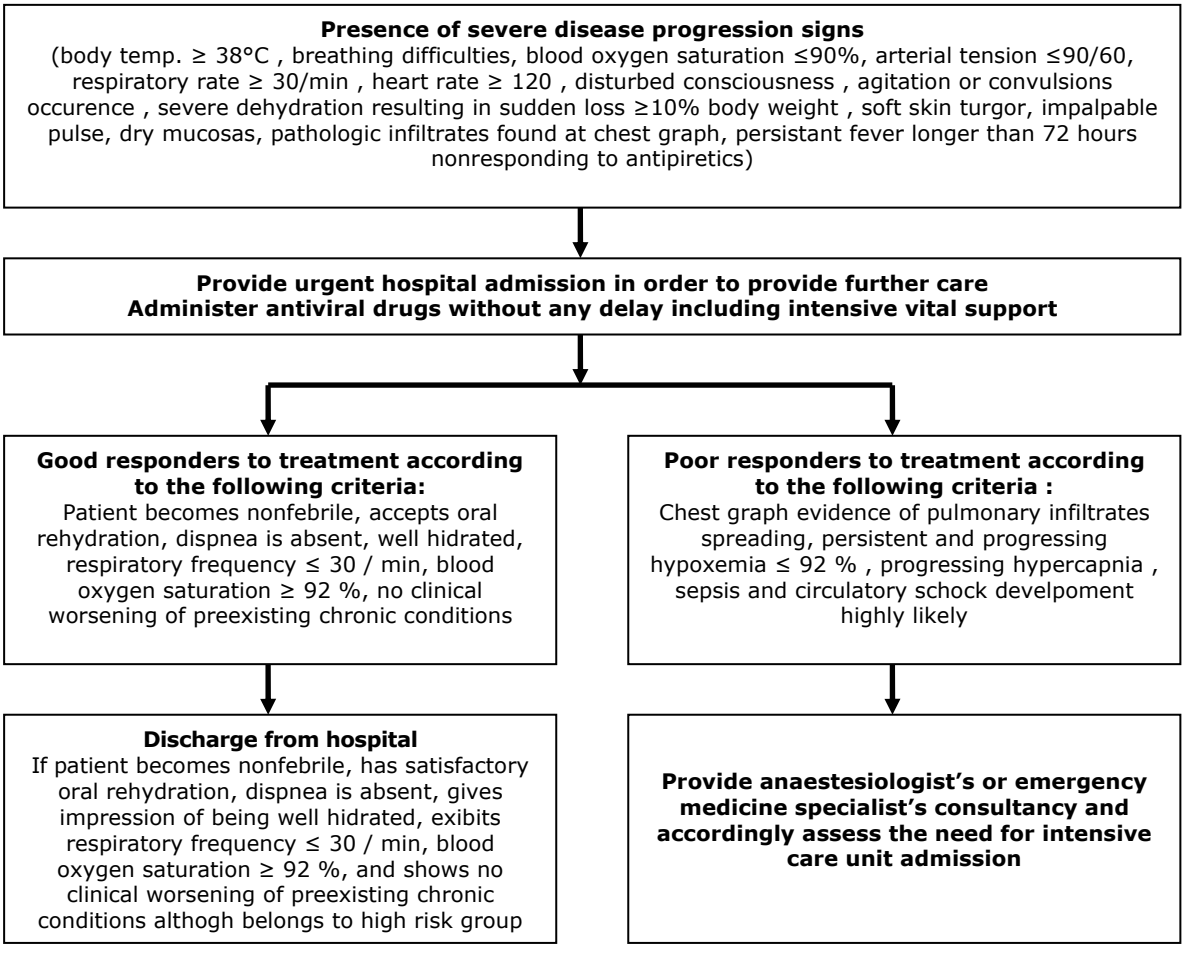


Table 1. Dosing regimen of neuraminidasis inhibitors, individualised in accordance with age and body weight

Five-day dosing regimen		
OSELTAMIVIR		
Body weight	Child ≥ 12 months	Adults
≤ 15 kg	30 mg per each 12 hours	75 mg per each 12 hours
15 - 23 kg	45 mg per each 12 hours	
23 - 40 kg	60 mg per each 12 hours	
≥ 40 kg	75 mg per each 12 hours	
Child from 0 to 12 months age		
	3 mg / kg per each 12 hours	
ZANAMIVIR		
	Children older than seven	Adults
	10 mg per each 12 hours (twice inhaled by 5 mg)	10 mg per each 12 hours (twice inhaled by 5 mg)
PERAMIVIR (FDA has approved intravenous drug in highly restricted indications because safety and efficacy are not confirmed with significant level of evidence)		
* Vitaly endangered adults are considered suitable for peramivir application or pediatric patients with unsatsifactory response to oral / inhaled neuraminidasis inhibitors treatment or expected bioavailability of drug falls within unacceptable levels due to clinical reasons or pure compliance		

Available treatment options

Summary of experiences in handling persons infected with pathogenic influenza viruses gives us several pharmacological alternatives available to silent clinical course of disease and provide complications to become more seldom:

1. Neuraminidasis inhibitors intake, which prevent adhering of viral capsid to the eukaryotic (e.g. mammal or human) cell membrane and „decoating" of RNA into cytosol. Different pharmaceutical markets, with different rate of success, had experiences with oseltamivir, zanamivir and peramivir, applied through several dosing regimes and routes of administration and consequently choice of drug forms used,
2. Bacterial super infections antibiotics treatment, most commonly situated in lower respiratory tract, according to available evidence-based guidelines on hospital acquired pneumonia management,
3. Low dose cortisol analogues are proper only with developed respiratory distress syndrome and together with neuraminidasis inhibitor. High doses are not recommended even as adjuvant therapy and have neither proven efficacy nor safety in this indication.

First choice treatments are certainly oseltamivir and zanamivir. The new influenza virus exhibits sensitivity towards these two medicines and resistance towards amantadin. Oseltamivir should be introduced in all patients with suspected or proven influenza virus infection. It is essential to begin as soon as possible after early symptoms (5). Dosing regimen of oseltamivir and zanamivir, individualized in accordance with age and body is noticed in Table 1.beneath (5):

Severe disease forms require oseltamivir doses of even 150 mg twice daily (4,6).

Chemoprophylaxis of exposed persons should be conducted 75 mg once or twice daily during first ten days from risky contact (7). Danger exists because of possible NA mutation and consequence of that change could be decreased viral sensitivity neuraminidasis inhibitors. Up to date research showed that H274Y mutation (histidine instead of tyrosine on position 274) at NA, induced in an experiment, leads to the decreased viral sensitivity towards oseltamivir carboxylate in vitro (8).

Quite frequent question is regarding should antibiotics necessary be introduced at all, in these viral infections. One of the brand features of this particular entity is the fact that bacterial pneumonia is one of the main clinical complications, commonly caused by meticillin resistant Staphylococcus aureus. These patients in most cases require assisted ventilation so that contributes to the risk of getting pneumonia. So we support an opinion that some chemotherapeutics should be included in treatment protocols dependable of the microbes found in the isolates. Former studies showed up that macrolides exhibit some relevant features for slowing down the pace of blood spreading of infection. Azithromycin seems to inhibit local inflammatory response for a few weeks. Never the less erythromycin administration 3,3 mg/kg/day raises survival rates in H2N2 inoculated lab mice. Erythromycin also shows substantially lower Interferon

gamma production from leucocytes in infected pulmonary tissue and portion of infected cells is lower after six of administration. Clarithromycin was reported to successfully cure childhood bronchiolitis caused by respiratory syncytial virus (7). Some other chemotherapeutics could be optional depending of the cause and its epidemiology. Chemoprophylaxis of bacterial infections before clinical signs and symptom occurrence is not supported by evidence. Well known fact of tetracycline', chloramphenicol and quinolones' teratogenicity forces us into caution when pregnancy matters or could happen in the meantime (4,9).

Oxygen therapy should be considered necessary part of treatment protocols in this area of indication. Pulse oximetry is common analytical method used to measure efficacy of gas exchange. Oxygen is applicable by nasal canula, oxygen mask with or without reservoir, endotracheal intubation or assisted ventilation and the method of choice is dictated by level of hypoxemia (5). Acute respiratory distress syndrome and some refractory hypoxemias can sustain and last although assisted ventilation is applied and sometimes we are forced to conduct veno – venous extra corporal membrane oxygenation. This method is kind of respiratory back up to the patients non-responding to the more conventional methods. Never the less we can not exclude the risk of acute hemolysis, hemorrhage and cardio-vascular instability (6,9).

According to the evidence based guidelines, routine corticosteroid administration is not recommended in this indication mostly due to weakened efficacy of cellular immune response caused by pharmacologically induced lymphocytes depletion in lymph nodes (4,5). Except this, it was noticed in clinical setting, that cortisol analogues can induce bacterial infection getting worse and even creating preconditions susceptible to sepsis (9). Never the less there is a precedent to this rule accounting for low doses methyl-prednisolone treatment combined with oseltamivir in patients with developed acute respiratory distress syndrome and initiated assisted ventilation. According to up to date research, current recommen-dation is initial 60 mg intravenous bolus dose, afterwards 60 mg/daily by means of continuous IV crystalloid solution infusions and 1-14 days duration, 30 mg/day and 15-21 day duration, 15 mg/day and 22-25 days duration,10 mg/day and 26-28 days duration. Unless overall patient physical condition gets worse or acute respiratory distress syndrome deepens dosing can be adjusted to 1mg/kg/daily (9,11).

If we consider non steroid anti inflammatory analgesics, mostly cyclooxigenasis inhibitors, febrile responses we commonly handle by para-cetamol as the safest one among them either in solid oral forms or suppositories in childhood. We should be aware of the risky salicylates usage in kids and youngsters due to possible hepatorenal acute insufficiency development (12).

Treatment and care of vulnerable patients

Medical care is certainly very important to successfully cure the flu symptoms. It assumes intensive care unit admissions, 24-hour monitoring of vital functions, follow-up of infection clinical and biochemical markers, prevention of complications' development especially regarding bacterial pneumonia and medical personal protection. A part of these efforts should be the symptoms' management. Different selected antipiretics exibit similar efficiency; however, ibuprofen is somewhat safer than diklofenak administered intravenously; as for aspirine, one should be cautious because of the Rey syndrome. Paracetamole, in some markets available in parenteral forms, remains the best tollerated among women and children.

Oseltamivir prescripition during pregnancy is allowed and even recommendable because of explicit and proven viral teratogenicity. In two hospital settings of Japan malformations rates of 1,1% were reported following oseltamivir first trimester intake per 90 pregnancies sample (one case in fact) and that's the general population frequency of fetal anomalies occurence (7). Ribavirin may not be used in pregnancy because data on high dosage regimens safety in this sense lacks (13).

During lactation, oseltamivir is being meta-bolised in milk. However, the babies are exposed only to some 0,012 mg/kg daily, what is a significantly lower common pediatric regimen (2-4 mg/kg daily) (7). Unless there is no possibility to administer oseltamivir, or the virus proves to be certainlu resistant, we may consider zanamivir application. Zanamivir is usually introduced in 10 mg, inhaled twice daily (5,14). We can administer it to the children more than seven years old. Ribavirin is also used in some healthcare systems but only in aerosol preparation and only combined with oseltamivir (15-17).

Probability of H1N1 strain spreading in future

Some forty years after the last one, humans were confronted to one of the most serious contemporary pandemic events. Although it seems that new cases' occurence is decreasing during the last months, true capabilities of this infectious disease are not easy to estimate at the moment (18). We can just hope that our previous similar experiences with the flu caused by A virus should be enough to prevent massive morbidity and mortality in our population. Vaccine remains the best weapon ever, but we must be aware of the raising level of clinical complications. It is crucial for us to be conscious of real posssibility to have new heavy flu caused burden to healthcare system if the autumn wave of infections takes place in 2010. In that sense, what matters is proper preparation by means of treatment guidelines dissemination. It is essential to provide the back up regarding antiviral treatment in this indication because of the uncertain prognosis and severity of clinical complications of this flue syndrome.

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RASPOLOŽIVI PRISTUPI U LEČENJU AKUTNE INFLUENCA H1N1 INFEKCIJE I NJENIH KLINIČKIH KOMPLIKACIJA

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Pandemija novim sojem H1N1 influenca A adenovirusa u humanoj populaciji razvila se iz originalno lokalizovane meksičke infekcije s proleća 2009. godine. Čini se da se sadašnji talas infekcija polako seli ka južnoj hemisferi ali obaveštenja Svetske zdravstvene organizacije o aktivnim žarištima u Jugoistočnoj Aziji, Zapadnoj Africi i tropskom ostrvlju Srednje Amerike ne isključuju ponovni talas obolevanja na našim geografskim širinama. Pojava je privukla pažnju epidemiologa i virusologa činjenicom da je u pitanju antigenski drugačiji kapsid koji eksprimira belančevine poreklom od genoma humane, svinjske i ptičje influence i nije pokriven raspoloživim sezonskim vakcinama. Takođe, iako oboljenje većinom protiče pod klasičnom kliničkom slikom influence, osobenosti su pridodata značajna gastrointestinalna simptomatologija i ranjivost mlade populacije. Kod malog ali značajnog procenta obolelih zapažen je prognostički loš tok, sa naglim razvojem respiratorne insuficijencije i poremećaja svesti koji zahtevaju intenzivan nadzor i lečenje. Citokinsku oluju bi svakako trebalo pomenuti kao jedan od ključnih patogenih činilaca koji opredeljuju mortalitet značajnog procenta teško obolelih. Ukoliko izuzmemo aktivnu imunizaciju kao prilično efikasnu meru prevencije, ostaju nedoumice kliničara kako lečiti komplikovani tok aktivne infekcije. Podsetimo se da su supstance prvog izbora u kauzalnoj terapiji, na koje je uzročnik dokazano senzitivan, inhibitori neuraminidaze - oseltamivir na koji je zapažena mestimična rezistencija i zanamivir do sada uvek delotvoran, kao i intravenski peramivir, čije mesto u terapiji još uvek nije sasvim utvrđeno. Uspeh direktne antivirusne terapije je zapažen i posredstvom lokalno primenjenog sintetskog nukleozida u aerosolu - ribavirina. Superponiranu bakterijsku pneumoniju ćemo najčešće lečiti prema utvrđenim principima lečenja bolničke pneumonije za koju danas postoje i vodiči dobre prakse zasnovani na dokazima. Ipak, podsetićemo se da septična infekcija pluća multirezistentnim klicama, bez obzira na intenzivno lečenje, ostaje vodeći činilac mortaliteta teških kliničkih prezentacija influenze H1N1. *Acta Medica Medianae 2010;49(3):76-82.*

***Ključne reči**: Influenza H1N1, lečenje, virostatici, pandemija*