INFLUENZA. CLINICAL PICTURE. PREVENTION AND TREATMENT

GRYPA. OBRAZ KLINICZNY. ZAPOBIEGANIE I LECZENIE

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SUMMARY

One of the most contagious diseases is influenza. It can affect everybody, without reference to age or race. As a matter of fact, there is no other acute respiratory disease which spreads as fast and extensively as influenza in human population. In the history of influenza we can find not only epidemic occurrences, but also big malignant pandemics. Antigenic drift is caused by very small point mutations. The result of such a change is a new variant of a virus which only slightly differs from the variant circulating in population from the previous year and it is the cause of epidemic occurrences. A pandemic spread of influenza virus is caused by a change of one or both surface antigens.
Such a fundamental change is characterized as an antigenic shift and it is considered a specialty of type A influenza virus. Proved by experience South-East Asia might be considered as an endemic area of the occurrence of animal, mainly avian influenza strains, which induced repeated infections also in humans with a high mortality rate as a consequence. Each case of an influenza A (H5N1) virus transmission to humans is a reason to worry, because anytime the virus can adapt to inter-human transmission. Since 2003 the spread of avian influenza in South-East Asia induced by influenza A (H5N1) virus has been the reason to worry because a new subtype of influenza virus can appear and this can initiate spread of disorders in humans and cause a pandemic. Currently, influenza can be a big risk causing serious disorders mainly in older people and chronically ill patients. An important attention of an ambulatory practice is necessary to put in especially to either primary or secondary influenza complications. It is appropriate to send a patient to a bed facility as soon as possible when primary complications appear. At secondary bacterial complications a patient should be given antibiotics or be hospitalized after the evaluation of a risky state of the patient.
When talking about a therapy of influenza a symptomatic treatment is on the first place. In some cases, mainly among risk patients administration of antiviral agents could be useful. Broader use of antiviral agents is limited by their price and accessibility of individual medications. The most important precaution of influenza prevention is vaccination. Prophylactic application of antiviral agents is limited to rare cases; however, such treatment can become very important during a pandemic.

Key words: influenza, avian influenza, clinical manifestations and symptoms, antiviral treatment, vaccination.

STRESZCZENIE

Jedną z najbardziej zaraźliwych chorób jest grypa. Może ona dotknąć każdego, bez względu na wiek i rasę. Prawdę mówiąc, nie ma żadnej innej choroby, która rozprzestrzenia się tak rozlegle jak grypa w populacji ludzkiej. W historii występowania grypy możemy odnaleźć nie tylko zjawiska epidemii, lecz również duże, złośliwe pandemie. Tendencja antygenowa jest spowodowana poprzez bardzo małe mutacje genowe. Wynikiem takiej zmiany jest nowa odmiana wirusa, która zaledwie w niewielki sposób różni się od odmiennego wirusa krążącego w populacji od ostatniego roku i jest przyczyną występowania epidemii. Pandemiczne rozprzestrzenianie się wirusa grypy jest spowodowane przez zmianę jednej bądź obu powierzchni antygenów.
Tak fundamentalna zmiana jest scharakteryzowana jako antygenowe przesunięcie i jest uważana za specjalność wirusa grypy typu A. Dowodem jest wystąpienie ptasiej grypy w południowo-wschodniej Azji, które wywołało powtórzone infekcje także u ludzi z dużym odsetkiem umieralności. W każdym przypadku grypy A (H5N1) przenoszenie wirusa na ludzi jest powodem do niepokoju, ponieważ w każdej chwili wirus może zaadaptować się do przenoszenia między ludźmi. Od 2003 roku rozprzestrzenianie się ptasiej grypy w południowo-wschodniej Azji wywołane przez wirus A (H5N1) jest powodem do obaw, ponieważ może się pojawić nowy podtyp wirusa grypy, a to z kolei może zainicjować rozprzestrzenianie się dolegliwości u ludzi i spowodować pandemię. Obecnie grypa może powodować poważne dolegliwości głównie u starszych oraz przewlekle chorych ludzi. Należy zwrócić szczególną uwagę zarówno w początkowych, jak i zaawansowanych powikłaniach grypowych. Właściwe jest, by przy pierwszych powikłaniach grypy jak najszybciej zastosować leżenie w łóżku. W przypadku zaawansowanych powikłań bakteryjnych pacjent powinien przyjąć antybiotyki lub być hospitalizowany po odpowiedniej ocenie stanu zdrowia.
Pierwsze miejsce powinno zajmować leczenie objawowe. W niektórych przypadkach podawanie środków przeciwwirusowych, głównie pacjentom z ryzykiem, byłoby pożyteczne. Szersze użycie środków przeciwwirusowych przy indywidualnym leczeniu jest ograniczone przez ich cenę oraz dostępność. Najważniejszym środkiem ostrożności przy zapobieganiu grypie jest szczepienie. Zapobiegawcze zastosowanie środków przeciwwirusowych jest ograniczane do rzadkich przypadków, jednakże takie leczenie może stać się bardzo ważne podczas pandemii.

Słowa kluczowe: grypa, ptasia grypa, objawy kliniczne i symptomy, leczenie przeciwwirusowe, szczepienie.

INTRODUCTION

Influenza, having a great impact on mankind for centuries, is a highly contagious viral disease affecting the respiratory system and overall it has very distinct symptoms.

First description of clinical signs about an epidemic goes back to 412 before Christ from Hippocrates. Some theories say that so called plague cataclysm, which struck Athens during Peloponnesian war was in fact a flu epidemic [1]. The name – "influenza" is dated from the 15thcentury in Italy. Those days the origin of the infection was laid the blame on the influence of stars (Influence = Influenza). Later Italian authors called influenza "influenza di freddo" (cold weather should have had an influence on initiation of a disease). In 1742–1743 the British also introduced the name during the epidemic and by coincidence the French started to call this disease "La grippe".

In winter months, almost every year, it causes epidemic of various range. Except a great number of illnesses and their possible complications it causes significant economic losses [2, 3]. However, nowadays substances with proven antiviral effects against the influenza virus exist. It is possible to use them for prevention, too. Vaccination remains the most important precaution against this disease, or at least its adverse consequences [3, 4]. In case of an outbreak of the disease, early diagnosing of influenza plays an important role mainly for identification of an optimal treatment course to avoid severe progress of the disease, which can appear mainly among risk groups of patients [5].

What's the origin of the influenza infection?

Influenza virus [1] is the originator of flu both "human" and "bird". Influenza viruses belong to the family Orthomyxoviridae and are divided into three types of viruses – influenza A, B and C (see tab. 1).

Table l. Brief characteristic of influenza viruses

Type A Influenza Virus	Type B Influenza Virus	Type C Influenza Virus
16 hemagglutinin subtypes	Only 1 type	Only 1 type
9 neuraminidase subtypes	Drift	Drift
Animal reservoir Shift, drift	No animal reservoir Has no pandemic potential	No animal reservoir Clinical, mild symptoms
Epidemiologically the most severe		Has no pandemic potential Epidemiologically the least severe

Only type A influenza virus has demonstrable animal reservoir – exceptionally numerous population of migratory waterfowl (see tab. 2). In this varied environment the influenza virus can occur in sixteen subtypes, the number of which has been set by different variants of an important surface antigen called "hemagglutinin". Hemagglutinin is responsible for binding the influenza virus to the surface of a perceived cell.

The second surface antigen called **"neuraminidase"** has been known in nine subtypes up to now; it has characteristics of an enzyme and its main task is to release an already complete viral particle from the affected cell and a foray of the virus through a slime layer on a mucous membrane to another perceived cell. Influenza virus has a gene, consisting of eight free segments of viral RNA. This characteristic along with the existence of the animal reservoir brings in a possibility of a mutual exchange of some segments when a dual infection of one cell of the virus of different subtypes develops and that can result in formation of epidemiologically dangerous variants. This process called "re-assortment" explains a mechanism of so called **"antigenic shift".** In terms of epidemiology of the human influenza it carries along the formation of so called pandemic strain, or a new subtype, with which the population did not have immunity until then and against which a general perception exists. So called "antigenic shift" introduces only small changes within a subtype (point mutations), which are stipulated by selective pressure of antibodies. Nowadays common seasonal flu is caused by subtypes H1N1 and H3N2.

Table 2. Natural hosts of type A influenza virus

Natural hosts of type A influenza virus			
hemagglutinin		neuraminidase	
Name	Host	Name	Host
H1	humans, pigs, birds	N1	humans, pigs, birds
H2	humans, pigs, birds	N2	Humans, pigs, birds
H3	humans, pigs, birds	N3	birds
H4	birds	N4	birds
H5*	birds (humans)	N5	birds
H6	birds	N6	birds
H7*	birds, horses (humans)	N7	horses, birds
H8	birds	N8	horses, birds
H9	birds (humans)	N9	birds
H10–H16	birds		

*only subtypes H5 and H7 can occur in a high or low pathogenic form; other subtypes belong to low pathogenic forms

Clinical manifestations and symptoms

We often come across the fact that common infections induced by different respiratory viruses which are accompanied by problems with upper airways, but predominantly without any serious overall symptoms, are wrongly qualified as influenza. On the contrary immediate **fever**, distinct **overall symptoms** and **catarrh of airways** are typical for flu. Incubation period is short (from some hours up to 2 days). Clinical signs of influenza (see tab. 3) can appear suddenly, and a patient can often exactly define an hour of starting to feel ill.

Table 3. Clinical picture during influenza

Overall symptoms	Respiratory symptoms	Other symptoms
Flash start	Cough	Headaches
Fever	Acute respiratory distress	Conjunctivitis
Chill	Sore throat	Loss of appetite
Myalgia	Rhinitis or Cold	Stomachache
Arthralgias	Sputum expectorant	Vomiting
Weakness		Diarrhea
Malaise		

We can observe a fast fever rise, more than 39 ºC at the beginning of the illness accompanied by chill, muscle aches, aches of extremities or back aches, aches in calves especially in children, but also headaches, mainly in a part behind eyes. Other overall symptoms such as malaise, fatigue and a loss of appetite can be present. Exceptionally gastrointestinal distress, nausea and meningeal syndrome do not occur. In the clinical picture mostly headaches and muscle aches are dominant, and their intensity corresponds with the fever. Conjunctivitis is often associated with weeping, an eye smart and a strong pain of eye muscles. Arthralgias are also quite frequent, but symptoms of a real arthritis are not present. Overall disorder lasts in average three days; it is same with the fever which reaches its peak usually within twelve hours from the start. The fever has mostly continual character, but it can be intermittent mainly when a patient is on antipyretic medications. It goes down gradually the second and the third day by 0, 5–1ºC. The fever lasts between 1–5 days, very rarely longer [6]. Patient looks toxic, the face is red, the skin is warm and wet; eyes weep, conjunctivitis occurs, clear secretion comes out of the nose, mucous membranes of the nose and the throat are hyperemic. Throat lymph glands are usually slightly swollen.

Respiratory tract problems, mainly dry and hypergic cough, ardour in the throat, problems to swallow and flux coming out of the nose are frequent from a very beginning of the disease. Overall symptoms are highly dominant over the above mentioned symptoms, which is typical for influenza unlike other infections of the upper airways. To become hoarse and a sore throat are more conspicuous after a regression of the overall symptoms and last 3–4 days after the fever descent. Cough is the most frequent and annoying among all the problems and aches along with ardour in chest. A stadium of convalescent until a complete recovery takes 1–2 weeks and except the cough the longest lasting is weakness and malaise. However, more direct or indirect methods to prove the infection of influenza virus, most cases, especially during the season, are diagnosed only according to the clinical picture and known epidemiological situation.

Course and Complications

The course of infection caused by the influenza virus can have a different intensity with different intensity of clinical manifestations – from asymptomatic infections, through a mild disorder, to the cases of typical manifestations of flu. A course of the disease can be very serious mainly in older people and the people with chronic disorders in which complications or even lethality occur much more often (tab. 4). Sometimes in older people only high fever, fatigue or confusion without the typical manifestations of airways can occur. The diseases caused by type B influenza virus are usually a bit milder than infections caused by type A influenza virus. Type C influenza virus has symptoms similar to common cold; it is not accompanied by fevers or overall symptoms and does not induce epidemics [5].

Table 4. Persons at increased risk of influenza – related complications and mortality

- Persons older than 65
- Medical staff of ambulatory facilities with the frequency more than 30 people per day, including general practitioners
- Medical staff in big hospitals, medical institutions for ill health patients and old people's home
- Patients from medical institutions for ill heath people without reference to age
- Residents of old people's houses
- Adults and children with chronic cardiovascular or respiratory disorders
- Adults and children watched by doctors because of metabolic or renal disorders, for hemoglobinophaty or immunosuppressive states
- Children and adolescents (6 months to 18 years of age) who are receiving long-term acetylsalicylic acid therapy and, therefore, might be at risk for developing Reye syndrome after influenza

In the course of flu more complications can occur (tab. 5). These are caused primarily by influenza virus or secondarily most often by the bacterial infection. **Primary** complications include influenza-like interstitial pneumonia with an exacerbation of cough, breathlessness or even respiratory insufficiency. The prognosis is serious, accompanied by high lethality.

In children stenotic laryngotracheobronchitis can be associated. Non-respiratory complications include myositis with myoglobinuria, myocarditis, pericarditis, polyradiculitis, myelitis and encephalitis. Reye syndrome observed in children mainly when treated with acetylsalicylic acid during influenza infection caused by type B influenza virus is considered a very serious complication, too.

Secondary complications include respiratory tract distress, mainly bronchopneumonia, bronchitis, sinusitis and otitis media. Most frequently secondary bacterial pneumonia during flu is caused by Streptoccoccus pneumoniae, Haemophilus influenzae and Staphylococcus aureus, more seldom by other gram-negative microorganisms.

Table 5. Complications

Respiratory		Non-respiratory
Primary	Secondary	
• Primary influenza-like pneumonia	• Secondary bacterial pneumonia	• Reye syndrome • Myositis and Myoglobinuria
• Acute stenotic laryngo-tracheobronchitis	• Exacerbation of chronic bronchitis • Sinusitis • Otitis	• Polyradiculo-neuritis • Myocarditis and Pericarditis • Encephalitis and Myelitis • Febrile spasms

Influenza treatment

If a patient has an uncomplicated flu without any other serious disorders, a symptomatic treatment is sufficient. In this case the patient needs a rest; drink enough of fluids and an administration of antipyretic medications. If the period of influenza symptoms is shorter than 48 hours, antiviral treatment can be considered, too. Because of the risk for developing Reye syndrome from antipyretic medications in children, we rather use paracetamol. Administration of antitussics in initial phase of the disease is not recommended, because they do not let secretions from airways go when ciliary functions are seriously damaged. The overall period of the convalescent should be 1–2 weeks.

We do not apply **antibiotics** at primary influenza infection. We also do not treat with antibiotics the acute tracheitis or tracheobronchitis, which are usually a part of the clinical picture of the primary influenza infection. Very often during influenza infection exacerbation of chronic obstructive disorder of lungs occurs. Antibiotics are recommended only when at least one of three conditions is fulfilled: exacerbation of cough and breathlessness, bigger volume and viscosity of sputum or a change of a sputum character to septic. We treat secondary influenza complications by antibiotics empirically consistent with the standard procedures for bacterial infections' treatment of respiratory tract. For a following procedure a current microbiological finding along with a clinical state of the patient is authoritative with a consideration of his/her hospitalization. Under the suspicion of the secondary bacterial infection antibiotics must be applied. When primary complications appear a complex treatment in a bed facility is appropriate [7].

During influenza epidemic **treatment and prophylaxis by antiviral agents** is recommended mainly in highly risk patients (tab. 3). It is important to consider the intensity of the symptoms, duration, but also presence of other serious disorders before making a decision about an antiviral agent treatment and a necessity of hospitalization [5]. Application of antiviral agents to a group of people, who can easily transmit influenza virus to risk groups, especially their relatives and personnel of medical facilities, could be a contribution from a medical and social view, too. From the time point of view it is necessary to start treatment as soon as possible. We indicate if the disease lasts less than 48 hours.

Currently, 2 groups of antiviral agents against influenza virus which differ by a mechanism of the effect are known. First group make **inhibitors of a canal protein M2.** Their mechanism of the effect lies in prohibiting of a case opening of the virus. They are effective only at type A influenza virus. The representatives of this group are amantadine and rimantadine. Their effect during the treatment is documented in several studies. These point out to a reduction of clinical symptoms and a faster fever descent if a reduction of the virus secretion duration in comparison to placebo [8, 9]. **Amantadine** and **rimantadine** absorb very well after an oral use. The secretion of amantadine is through urine and it does not change its form. Because of its more limited therapeutic index when applied it is important to consider a relatively small reduction of renal function, too [4]. Among its contraindications belong: hypersensitiveness to the agent, bigger liver dysfunction, heart 0, insufficiency, epilepsy, ulcerous disorders and more serious psychosis. Amantadine is used also as an anti-Parkinson agent because it blocks dopamine receptors [7]. Rimantadine is a derivative of amantadine with the same effect, but with much better tolerance. It is metabolized mostly in liver with a subsequent renal secretion of metabolites. His disadvantage is a faster development of the resistance [4, 10].

Neuraminidase inhibitors make the second newer group of the antiviral agents effective against the influenza virus. They prevent a formation of neuraminidase and by that make impossible for new incipient viruses to infect other epithelial cells. They are effective against both influenza A and B viruses. Representatives of this group are zanamivir and oseltamivir [7]. Neuraminidase inhibitors treatment shortens duration of the disease by 1–2 days, catalyzes a decline

Table 6. Antiviral agents used for treatment of influenza virus

Agent	Effect to influenza virus	Dosage	Dosage adjustment during renal insufficiency	Medication	Form
Amantadine	Type A	2×100 mg 5–7 days	With creatine clearance less than 50–80 ml/min	Viregyt-K PK- Merz	capsules, tablets
Rimantadine	Type A	2×100 mg 5–7 days	Not necessary	Flumadine Remantadine	tablets syrup
Zanamivir	Type A a B	2×10 mg 5 days	Not necessary	Relenza	inhalers
Oseltamivir	Type A a B	2×75 mg 5 days	With creatine clearance less than 30 ml/min	Tamiflu	tablets

of individual clinical symptoms of the disease and can also decrease the occurrence of secondary complications [11, 12]. Some other studies have shown that zanamivir and oseltamivir also decrease a degree and duration of virus secretion [13, 14].

Zanamivir is usually applied by oral inhaling into airways considering its low biological accessibility after an oral administration, and so it affects directly on the place of the highest activity of the infection, specifically, selectively and extra cellularly. It is not metabolized in the organism and it is secreted by kidneys. During a serious renal or jecoral disorder it is not necessary to reduce its dosage [4]. It is well tolerated and side effects are not usually serious if in patients with the associated lung disorder bronchospasms have been described [3]. Considering a lack of experience it is recommended to apply it only to adults and children > 7 years of age.

Oseltamivir has a high biological accessibility after an oral administration. It is secreted by kidneys in unchanged form, and it is therefore necessary a dosage adjustment of the medication. It is used in adults and children at the age of 13 and older. Side effects are most frequent from the side of a gastrointestinal tract [4, 7]. A table 6 shows the summary of antiviral agents.

Prevention and prophylaxis

Prevention by vaccination remains the most important tool when fighting against influenza in spite of new treatment possibilities. **Vaccination against influenza** has been used since 40s of the last century and even currently introduces a main precaution for influenza control. All currently used vaccines are **trivalent.** In the last years contain antigens of two strains of type A influenza virus (H1N1 and H3N2) and one type B influenza virus. There is a development of vaccines every year to ensure the presence of concrete strains expected the following season. On the North hemisphere (hence in our conditions) an optimal vaccination period is from October to a half of November. Immunity can develop within two weeks after vaccinations and a protection continues for following 4–6 months [3]. Inactive vaccine can be applied to adults and children older than 6 months. Vaccination of **persons at increased risk of complications** (mentioned above; tab 4), and their contacts, similarly to indication of antiviral agent therapy, is of the exceptional importance. Currently, the age limit for vaccination moves from 65 years to 50, considering relatively high occurrence of associated serious disorders mainly in this age group. Vaccines' effectiveness is relatively high and reaches 70–90%. It is possible to apply influenza vaccine along with other vaccines, for instance most often with a pneumococcus one [15]. **Adverse reactions** at vaccination **are rare** and usually not serious. When judging them it is necessary to realize that inactivated vaccines do not contain a live virus and therefore cannot induce flu, however, some of the adverse reactions could look like flu. During a flu season it is also necessary to recon with respiratory disorders induced by other pathogens which have no connection to vaccination. The benefit from vaccination of asthmatic patients considerably exceeds possible risks of the occurrence of accessions or bronchospasm [16]. Allergic reactions, exceptionally even anaphylactic shock or possible neurological complications belong among severe complications. A connection of Guillain – Barre syndrome with vaccination against flu also became a subject of the research, but unfortunately hasn't been confirmed so far.

Another possibility for flu prevention is **chemoprophylaxis by antiviral agents**. It is limited by costs and a patient cooperation, but in certain situations can be rational. It can be useful in patients at high risk of morbidity who came to contact with flu or were vaccinated just shortly before a start of the epidemic. **In case of a pandemic caused by a virus strain which the vaccine did not contain** the use of prophylactic antiviral agents could be also important [3]. It is possible to use all the antiviral agents for prophylaxis (see tab. 6). Standard therapeutic dosage of amantadine and

rimantadine, inhibitors of the canal protein M2, are used and they are effective only against type A influenza virus. Oseltamivir is applied in lower dosage, 75 mg/day [15]. Zanamivir is not usually used for prophylaxis; however, at post exposure prophylaxis it is appropriate to apply it (5mg/10 days; 7).

CONCLUSION

Despite initiation of effective vaccination and modern therapeutic approaches, influenza further remains a medical and economic problem. First antiviral agents: amantadine and rimantadine for treatment and prevention of influenza are effective against type A influenza virus and their use is limited by a growth of resistance and adverse reaction. Newer antiviral agents, neuraminidase inhibitors are effective against influenza A and B. Here belongs zanamivir, which administration is intranasal, and oseltamivir stipulated for oral use. In most uncomplicated cases of flu, treatment remains symptomatic. It is important to pay close attention to often very severe complications of flu, too. When primary complications occur it is appropriate to send a patient to a bed facility. At secondary bacterial complications it is necessary, according to a risk at a patient, to indicate antibiotics ambulatory or send him/her to a hospital. When it comes to prevention vaccination is still of a biggest importance. Recently the development of new vaccines and their applicatory forms contributed to considerable reduction of reactogenecity of vaccines keeping their protective effect.

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