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Influenza and the Vocal Performer: Update on Prevention and Treatment

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Summary: Upper respiratory tract infections (URIs) are a major cause of morbidity among vocal arts professionals, both from their acute impairment of the vocal mechanism and their predisposing influence for the development of serious vocal sequelae. In this review, we present some of the salient features of currently available treatments effective against influenza, the virus family responsible for the most serious form of URI. At present, these include an inactivated vaccine and four antiviral drugs, each approved in the United States and many other countries for the prevention and treatment of influenza. A live attenuated vaccine is also available, and other vaccines and antiviral drugs are under development. This review details the current options available for treating both influenza and noninfluenza related URIs in the professional voice user.

Key Words: Upper respiratory tract infection—Influenza—Singer—Vocal arts performer—Amantadine—Rimantidine—Zanamivir—Oseltamivir—Ion channel blockers—Neuramidase inhibitors.

INTRODUCTION

Upper respiratory tract infection (URI) is a non-specific term used to describe acute infections involving the nose, paranasal sinuses, pharynx, larynx, trachea, and bronchi. The prototype is the illness known as the common cold. Patients with an URI develop sore throat, fever, and hoarseness, making what would be an inconvenience to most

individuals, potentially crippling for the vocal arts performer.¹ Even minor URI-related symptoms can lead to alterations in voice quality, vocal fatigue, and reduced vocal range.² Moreover, the laryngeal inflammation resulting from an URI can predispose singers to mucosal disruption and hemorrhage—resulting in long-term, potentially disastrous, sequelae for the vocal professional.³ Viruses cause most URIs, with rhinovirus, parainfluenza virus, coronavirus, adenovirus, respiratory syncytial virus, coxsackievirus, and influenza virus accounting for most cases. Adults develop, on average, two to four URIs per year, with most occurring during the winter months.⁴ Compared to URIs caused by other viruses, influenza, is a more systemic illness, with the upper respiratory tract being only one of multiple organ systems involved. It should be recognized as distinct from other causes of URI.

Given the serious nature of viral URIs to singers, a thorough understanding of the clinical use of

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antiviral treatment options is advisable by the voice care professional. Antiviral treatment can be categorized into vaccines, prophylactic, and treatment medications.

INFLUENZA EPIDEMIOLOGY

Influenza rapidly spreads around the world in seasonal epidemics, imposing considerable economic burden in the form of health care costs and lost productivity. Pandemics are the most dramatic presentation of influenza. Major genetic changes in the virus have caused three influenza pandemic in the 20th century, killing many millions of people. The name comes from the old medical belief that unfavorable *influences* cause the disease.

Influenza reaches peak prevalence in winter, and, because the Northern and Southern Hemisphere have winter at different times of the year, there are actually two flu seasons each year. Hope-Simpson observed that influenza outbreaks are globally ubiquitous and consistently occur every 6 months following the time of maximum solar radiation in an area.⁵ Therefore, the World Health Organization makes two vaccine formulations every year, one for the Northern and one for the Southern Hemisphere.

While most influenza outbreaks in the Northern Hemisphere tend to peak in January or February, not all do. For example, the influenza pandemic of 1918 and 1919 reached peak virulence during late spring and summer worldwide, and not until October in the United States.⁶ It remains unclear why outbreaks of influenza occur seasonally rather than uniformly throughout the year. One possible explanation is that, because people are indoors more often during the winter, they are in close contact more often and this is enough to trigger the outbreak. Another is that the cold weakens the immune system; however, the virus is contracted in a warm indoor environment in which it can thrive.

ANTIVIRAL TREATMENT OPTIONS

Commercially available specific antiviral therapy agents are limited in number and, heretofore, aimed exclusively at the influenza family of viruses. Their indications and side effect profiles should be well

understood. Ion-channel blocker medications are a class of agents, which includes amantadine and rimantadine, and a newer class of agents, the neuraminidase inhibitors, which includes zanamivir and oseltamivir, have all been proven to be effective for influenza infection. Although there are currently no approved agents for the treatment of noninfluenza URI, one very promising antirhinovirus agent, pleconaril, is close to receiving US government approval for sale.⁷ This is a viral entry blocker, which blocks a pocket on the surface of the rhinovirus that controls the uncoating process. Finally, a trademarked elderberry extract (Sambucol; Razei Bar, Jerusalem, Israel), may aid in shortening the duration of an episode of influenza once contracted, though it has no notable preventive effects.⁸

Ion-channel blockers

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A viruses are further categorized into subtypes on the basis of two surface antigens: hemagglutinin and neuraminidase. Influenza B viruses are not categorized into subtypes. Since 1977, influenza A H1N1, influenza A H3N2, and influenza B viruses have been in global circulation. In 2001, influenza A (H1N2) viruses that probably emerged after genetic reassortment between human A (H3N2) and A (H1N1) viruses began circulating widely. Both influenza A and B viruses are further separated into groups on the basis of antigenic characteristics. New influenza virus variants result from frequent antigenic change (ie, antigenic drift), resulting from point mutations that occur during viral replication. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses.

Amantadine (Symmetrel; Endo Pharmaceuticals, Inc., Chadds Ford, PA) and rimantadine (Flumadine; Forest Pharmaceuticals, St. Louis, MO) are active against type A influenza virus only. They are approved for the prophylaxis and therapy of influenza A virus infection in the United States. If begun within 48 hours of the onset of illness, treatment with amantadine or rimantadine reduces the duration of systemic and respiratory symptoms of influenza by approximately 50%. These drugs

have been shown to be superior to antipyretic analgesics in this regard.⁹

The adverse reactions reported most frequently (5–10%) at the recommended dose of amantadine are nausea, dizziness, and insomnia. Less frequently (1–5%) reported adverse reactions are depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea, and fatigue. These adverse effects disappear promptly upon discontinuation of the drug. Rimantidine, although equally effective, is associated with less frequent central nervous system (CNS) side effects than amantadine. Adverse events reported most frequently (1–3%) at the recommended dose were nausea, insomnia, dizziness, headache, and nervousness.¹⁰

In adults, the usual dose of amantadine or rimantidine is 100 mg twice daily for 3–7 days. Treatment should be continued for 24–48 hours till the signs and symptoms disappear. Since both drugs are excreted via the kidneys, the dose should be reduced to 100 mg/day or less in elderly patients with renal insufficiency (Table 1).

For prophylaxis, these drugs must be administered daily throughout periods of highest risk for influenza infection. Studies have shown amantadine and rimantidine to be 70–100% effective in prophylaxis against influenza A.¹¹ Use of these medications may be particularly useful for healthy singers performing in an outbreak region, or with infected cast members, especially if they have not received influenza vaccine or if previously administered vaccines were relatively ineffective because of antigenic changes in the circulating virus. During an outbreak, amantadine can be used simultaneously with inactivated vaccine. In fact, there is evidence that the protective effects of amantadine and vaccine are additive.^{11–13} Amantadine may also be used in situations where a performer has had a known contact with an affected individual. For prophylaxis, amantadine or rimantidine should be administered promptly after a sick contact and must be continued for the duration of the local outbreak. The dosage for both amantadine and rimantidine is 200 mg/day for adults.

Neuramidase inhibitors

Zanamivir (Relenza) and oseltamivir (Tamiflu) are members of a new class of drugs termed neuraminidase inhibitors, which are active against both influenza virus type A and type B. These agents work by blocking the neuraminidase enzyme on the surface of the influenza virus (neuramidase facilitates the virus' spread from cell to cell in the respiratory tract).¹⁴ Zanamivir, as a dry powder is administered by inhalation twice a day for 5 days from a breath-activated device. Oseltamivir is available in pill form and is active against the A strain of the influenza virus, but has only minimal activity against the B strain. Clinical trials have shown that both agents need to be started within 48 hours of the onset of symptoms to impact the course of disease.¹⁵ Oseltamivir, but not zanamivir, is also approved for the prevention of influenza.¹⁶ In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults and adolescents, oseltamivir 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory confirmed clinical influenza from 4.8% for the placebo group to 1.2%.¹⁶ In a seasonal prevention study in elderly residents of nursing homes, 75 mg of oseltamivir taken once a day for 42 days reduced the incidence of laboratory confirmed clinical influenza from 4.4% for the placebo group to 0.4% for the oseltamivir group.¹⁷ Approximately 80% of this elderly population was vaccinated against the influenza. In a study of postexposure prevention in households, 75 mg of oseltamivir was given once daily within 2 days of onset of symptoms and continued for 7 days. Results of this study show oseltamivir reduced the incidence of laboratory confirmed clinical influenza from 12% in the placebo group to 1% in the oseltamivir group.¹⁸ Side effects from oseltamivir, when taken for prevention, were similar to those from patients who took the drug for treatment. The most common side effects were nausea, vomiting, headache, and fatigue. Efficacy of oseltamivir for the prevention of influenza has not been established in immunocompromised patients. Patients should continue receiving an annual influenza vaccination according to guidelines on immunization practices. Oseltamivir is not a substitute for the influenza vaccine.

TABLE 1. Antiviral Agents Active Against Influenza Virus

Drug Name	Indications	Dosage	Contraindications	Precautions	Interactions
Tamiflu (Oseltamivir)	Effective to treat influenza A or B*	Acute illness: 75 mg PO bid for 5 days Prophylaxis: 75 mg PO qd	Documented hypersensitivity	Caution in renal impairment, chronic cardiac or respiratory disease, and breastfeeding	None reported
Relenza (Zanamivir)	Effective against both influenza A and B	5-mg inhalation bid for 5 days	Documented hypersensitivity, obstructive airway disease	Monitor respiratory status; caution in breastfeeding	None reported
Flumadine (Rimantadine)	Indicated for both prophylaxis and acute treatments	Acute treatment: 100 mg PO bid Prophylaxis: 100 mg PO bid	Documented hypersensitivity	Resistant virus strains may develop and be transmitted. Caution in hepatic impairment	Acetaminophen and aspirin reduce levels when taken concurrently; cimetidine increases plasma levels when taken concomitantly
Symmetrel (Amantadine)	Indicated for both prophylaxis and acute treatments	<65 years: 200 mg/day PO qd or divided bid >65 years: 100 mg PO qd	Documented hypersensitivity	Resistant virus strains may develop and be transmitted [†]	Drugs with anticholinergic or CNS stimulant activity increase toxicity [‡]

Abbreviations: Bid, twice per day; PO, per oral; Qd, once.

*Must start medication within 48 hours of symptom onset. The best effect occurs the sooner it is taken after symptom onset.

[†]Caution in liver disease, and those receiving CNS stimulant drugs; CNS effects, Parkinson disease; do not discontinue abruptly.

[‡]Concurrent administration of hydrochlorothiazide plus triamterene with amantadine may increase plasma concentrations of amantadine.

PROPHYLAXIS

The major public health measure for prevention of influenza has been the use of inactivated influenza vaccines from influenza strains that circulated during the previous season. When the vaccine virus matches the previous years' circulating strain well, immunization can provide from 60% to 90% protection against influenza.¹⁹ Current vaccine formulations are highly purified and associated with few reactions. Up to 5% of individuals experience mild fevers and systemic symptoms 8–24 hours after injection, and a third of recipients will experience tenderness and erythema at the injection site. A live attenuated influenza A vaccine (FluMist; MedImmune Vaccines, Gaithersburg, MD) has

also been developed, which is administered intranasally and stimulates local antibody production more efficiently than conventional inactivated vaccines.²⁰ One placebo-controlled study in 103 experimentally infected adults found that the protective efficacy of FluMist was 85%, compared to 71% with inactivated influenza vaccine.²¹ Vaccination, by either method, becomes effective 10–14 days after administration. Because the live attenuated vaccine depends on the replication of the vaccine recipient in the nasopharynx, antiviral drugs for influenza should not be started for 2 weeks after receiving the vaccine.^{22–24} The most common side effects include cough, runny nose/nasal congestion, irritability, headaches, chills, muscle aches, and fever > 100° F. For adults, nasal congestion (9.2% FluMist vs 2.2%

placebo), rhinitis (6.3% FluMist vs 3.1% placebo), and sinusitis (4.1% FluMist vs 2.2% placebo) were reported significantly more often by FluMist recipients compared to placebo recipients.²⁵ Nasal congestion, runny nose, sore throat, headache, irritability, decreased activity, muscle ache, and cough are the most common adverse events associated with the vaccine. Of note, FluMist is contraindicated in adolescents receiving aspirin therapy or aspirin-containing therapy because of the association of Reye syndrome with aspirin and wild-type influenza infection. Also, FluMist should not be administered to individuals with a history of asthma or reactive airways disease. Intramuscularly administered inactivated influenza vaccines are available to immunize high-risk individuals.

RECOMMENDATION FOR SINGERS

Presented below is a summary, in outline form, of influenza treatment options available to professionals entrusted with the care of the professional voice. The listed treatments are organized according to the acuity of the need for intervention.

1. Prophylaxis: As with other diseases, prevention is the most effective strategy for professional voice users. This can take the form of either chemoprevention or vaccination:
 - a. Short-term chemoprevention is indicated under the following conditions
 - i. A 14-day course of prophylaxis should be considered for the 2-week interval following the immunization of performers when there is influenza activity in the community or performance troupe at the time of immunization.
 - ii. A 10-day course of prophylaxis should be considered for all individuals in the performance troupe with known contact with an index case of influenza.
 - b. An extended course of prophylaxis (to cover the entire period of significant influenza activity in the community) should be considered in selected settings:
 - i. Protection of singers for whom the vaccine is contraindicated (eg, singers with

a history of anaphylactic reaction to eggs)

- ii. Protection of immunized high-risk singers if vaccine strain poorly matches circulating influenza strains

Chemoprophylaxis can be accomplished with amantadine, rimantadine, zanamivir, or oseltamivir. Amantadine (200 mg/day orally in two divided doses, or 100 mg/day in those susceptible to CNS side effects) and rimantadine (200 mg/day in two divided doses) are effective only against influenza A. Oseltamivir (75 mg/day) and zanamivir (10 mg inhaled daily) are effective against influenza A and B. All the above medications will reduce the attack rate among unvaccinated individuals if begun shortly after exposure. Comparative trials among the agents have not been done.

- c. Vaccination is indicated in performers expecting to work in a city where there is an influenza outbreak.

Inactivated influenza vaccine can be concurrently administered if the singer is expected to reside in the influenza affected for more than 2 weeks. Live attenuated vaccination cannot, however, be coadministered with a chemoprophylaxis regimen since limited viral replication is necessary for this vaccination modality to be effective.

2. Acute treatment:
 - a. In most healthy people, influenza is cured in 7–10 days. The worst symptoms usually last 3–4 days. Affected singers without imminent important performances may prefer to rest, with only light voice use. Analgesics and a cough mixture may be used. Home treatment to ease symptoms and prevent complications is usually all that is needed.
 - b. For the singer with performance requirements, antiviral medications, when started within 48 hours of the onset of symptoms, can be taken to:
 - i. Reduce the severity and duration of symptoms caused by infection with influenza A or B virus.
 - ii. Shorten the length of the illness.
 - iii. Control outbreaks of the flu in the performance troupe.

iv. Reduce complications from the flu.

Amantadine or rimantadine, in the same doses as used for prophylaxis, appreciably decrease the duration of symptoms and signs. Rimantadine is preferred in patients with renal failure.

- c. Theoretically, corticosteroids as potent anti-inflammatory agents could be thought to effectively reduce nasal symptoms, but results of clinical studies of either intranasal or oral steroids have shown no clinical benefit.²⁶⁻²⁸

CONCLUSION

In addition to being a serious health threat to the public at large, influenza presents a potential source of significant morbidity for the vocal arts professional. This review has highlighted a number of interventions currently at the disposal of those charged with the care of the professional voice. Judicious use of preventative and therapeutic modalities, combined with careful follow-up will optimize vocal performance and, more importantly, prevent serious injury to the vocal mechanism. In future, continued improvements and refinements in the capacity to design effective vaccines combined with new, structure-based, drug design techniques will yield increasingly effective interventions. Until then, voice-preserving strategies must include timely vaccination combined with education of the vocal arts professional on how to recognize the early signs and symptoms of influenza so as to allow for the earliest possible initiation of antiviral therapy.

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