INFECTIOUS DISEASES

TREATING INFLUENZA IN THE EMERGENCY DEPARTMENT

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Patients frequently present to the emergency department (ED) with symptoms of influenza, the common cold, or a confusing combination of both symptoms. As most California emergency physicians know, these symptoms appear more frequently in the winter months when large sections of ED waiting rooms may be filled with flu or URI patients. It is sometimes difficult to distinguish between influenza and the "common cold." Influenza A and B are caused by an orthomyxovirus, whereas symptoms of the common cold can be caused by one of many viruses including rhinovirus, coronaviruses, RSV or adenovirus.[1] Influenza A is a zoonotic infection that also infects pigs, birds, horses, and seals. Indeed, the severe 1918 pandemic that resulted in millions of deaths worldwide is believed to have originated from pigs.[2]

Diagnosis: The following table has been utilized in some EDs to help discriminate between influenza and the common cold:

	INFLUENZA	COMMON COLD OR URI
Onset	Abrupt	Gradual
Fever	100-104° F	100° F or Less
Myalgias	Common	Occasional
Headache	Common	Variable
Rhinitis	Occasional	Common

The specificity and sensitivity of the above table have never been scientifically tested. Accurately diagnosing influenza A or B may be more difficult than the table above suggests. In addition to overlapping symptoms caused by "URI and Cold" viruses, other viruses cause influenza-like symptoms including enteroviruses, paramyxoviruses, and even "tropical" fevers such as Dengue. For example, 98% of persons who acquired West-Nile fever in New York in 1999 were initially diagnosed as having the flu.

The gold standard for diagnosing influenza A and B is a viral culture of nasal-pharyngeal and/or throat samples using dacron swabs which need to be sent in appropriate viral transport media (eg. M4 Transport Media) to the lab where it is cultured in several lines of cells. Diagnosis of influenza is made in the lab once specific cytopathic effect is observed or hemadsorption testing is positive. Confirmation is then performed using the infected cultured cell lines by staining them with fluorescent antibody. The process may take from three to seven days: long after the patient has left the ED and well past the time when drug therapy could be efficacious. Direct immunofluorescent tests on fresh specimens are also available in some labs, but are labor intensive and have sensitivity lower than culture methods. These tests require specially trained lab personnel for interpretation, not generally available all shifts, even in large medical centers.

In order to overcome this obstacle, several "bedside" tests have become available. In reality, many of these are not bedside tests as they generally require 30-60 minutes of time to perform multiple steps to complete the test.[3] "Rapid tests" are best done by a lab adjacent to the ED. Several disadvantages to performing these rapid diagnostic tests include the cost of the laboratory personnel to perform the test, the actual cost of the test itself, and the fact that the test may miss many patients who actually have influenza A or B. Test sensitivities are generally in the 60-70% range. Recently, the FDA waived Federal CLIA requirements and approved an actual ten minute "QuickVue" bedside test with 70-80% sensitivity. Because of cost, availability, and sensitivity issues most EM physicians diagnose influenza on clinical criteria alone.

Treatment. Prevention is the most effective treatment as with other diseases. The CDC has published recommendations for high risk groups who should be vaccinated, which includes all health care personnel.[4] Amantadine and rimantadine have been approved for use against influenza A for many years. These have generally not been popularly used in EDs. Disadvantages of these drugs includes lack of efficacy against influenza B, potential side effects, and rapid development of viral resistance.

Two new drugs have been marketed for treatment of influenza A and B recently. These are the neuraminidase inhibitors, oseltamivir and zanamivir. Oseltamivir is taken orally, 75 mg twice and zanamivir via an inhalation apparatus, 10mg twice a day.[5] Multiple studies have demonstrated their efficacy. These agents work by inhibiting influenza virus neuraminidase, a glyco-protein spike on the outside of the virus envelope needed for successful cellular release and transmission within the body. These new agents need to be administered within 36 hours of onset of symptoms to be effective. Recent studies also show efficacy in the prophylactic use in preventing influenza A and B, an exciting expansion in use of these agents. The prophylactic dose is one-half the acute dose. There are several advantages to neuraminidase inhibitors compared with amantadine including less evolution of resistance, efficacy against influenza B, dramatic reduction in symptoms, even in patients who do have a full course of flu, and fewer side effects.

In a study of 445 patients by the Mist group 1, zanamivir was given to one-half and placebo to the others within 36 hours of symptom onset.[6] The duration of the flu was reduced by 1.5 days in normal groups and 2.5 days in high risk groups. A significant decrease in the severity of illness in patients treated with zanamivir allowed them to resume normal activities much sooner.

A recent study by Treanor compared oseltamivir to placebo.[7] This analysis included both with laboratory diagnoses of influenza as well as those with only clinical diagnoses based on symptoms. A total of 629 subjects were enrolled and randomized into one of three treatment arms: standard dose oseltamivir, "high dose" oseltamivir, and placebo. In both oseltamivir groups the mean illness duration was reduced from 103 to 70 hours. The symptom severity decreased in the treated group by 40%.

Additional studies analyzed the effect of neuraminidase inhibitors both in acute disease as well as in prevention.[8] In one of these studies, 837 relatives of sick family members who developed influenza were treated prophylactically with either placebo or zanamivir. While 20% of the placebo group became ill, only 4% of the drug-treated group became ill. In addition, this study also provided treatment to the index case family member and this resulted in a 2.5 day reduction in illness over placebo. DNA viral sequences were performed in this study and no resistant flu strains developed.

A novel study analyzed the effects of oseltamivir in human volunteers in an experimentally induced influenza.[9] In a controlled "laboratory" environment, these volunteers were directly inoculated intranasally with influenza A: Texas 36/91 HINI. One group had oseltamivir begun 26 hours before virus inoculation and another group 28 hours after inoculation. In the prophylactic group, 38% of patients developed influenza compared with 67% of placebo. In the post-treatment group, the duration of illness was reduced from 95 hours to 53 hours and the severity was reduced by 50% compared to placebo.

Treating Influenza continued

Finally, a recent study by Hayden analyzed 1,559 healthy, non-immunized patients who were treated either with placebo or oseltamivir for six weeks.[10] At the end of the six week period, 4.8% of the placebo group had laboratory confirmed flu compared with only 1.2% of the oseltamivir group. Additional studies are on-going analyzing both treatment efficacy as well as the profinitive effects of the neuraminidase inhibitors.

The decision by the EM physician on whether to prescribe one of the newer neuraminidase inhibitors should be individualized to the patient and the likelihood of actually having influenza A or B, and potential benefit that may occur. Advantages for prescribing these agents include a significant reduction in illness severity as well as reducing total illness duration. The elderly and high-risk patients also have decreased secondary complications of influenza when treated with these agents.

Disadvantages include potential side effects and costs. However, many patients are willing to pay $50 to have a less severe bout of the flu. Side effects include: 1) potential bronchospasm with inhaled zanamivir and, 2) nausea, vomiting and headache from oseltamivir. The bronchospasm associated with zanamivir has received attention from the national media. Until more data is available, physicians should not prescribe zanamivir to patients prone to bronchospasm.

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TOPICS IN TOXICOLOGY

CIGUATERA FISH POISONING

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Ciguatera poisoning is the most common foodborne illness related to fish consumption both within the United States and worldwide.[1] Ciguatera is found in a broad global belt within 35 degrees of latitude of the equator. Around the U.S., ciguatera is endemic in the Caribbean region, Mexico, Florida, Hawaii and other Pacific island territories. Since ciguatera is not a reportable public health disease, its epidemiology is not completely understood. Nevertheless, large common source epidemics have been described, including a recent series of 25 cases in Southern California Emergency Departments.[2] In Southern Florida, data suggest an annual incidence of five cases of ciguatera poisoning per 10,000 people, while the incidence rates in the South Pacific range up to 600 cases per 10,000.[3] Worldwide, it is estimated that over 25,000 people are affected by ciguatera fish poisoning annually.[4] Within California, local fish carry low risk, even those caught off of the Baja coast; whereas, higher risk fish imported from tropical waters might be found in any restaurant.

Ciguatera is an icthyosarcotoxicosis: food poisoning by the ingestion of toxin-contaminated fish meat. *Gambierdiscus toxicus* is the single-cell dinoflagellate that is responsible for the disease. It is believed that the presence of specific bacteria, phagocytized by the dinoflagellate, is required to synthesize ciguatoxin. *G. toxicus* attaches itself to dead coral surfaces and algae, and the toxins are passed up the food chain from small herbivorous fish to large carnivorous fish to larger predatory fish, and finally to man. The toxin load becomes concentrated as it moves up the food chain, although fish harboring the toxin do not appear to suffer ill effects. The proliferation of *G. toxicus* appears to be related to disturbances if the reef ecosystem. Toxic fish are more often found on the windward side of tropical islands where wave energy and storm damage are greater. Storms, floods, tidal waves, and man-made processes such as anchoring, mining, dredging, and military bombing all appear to increase proliferation of the organism.

Over 400 species of fish are associated with ciguatera poisoning. In the U.S., the greatest risk comes from consumption of grouper, red snapper, barracuda and jacks. Large, bottom-feeding, reef-dwelling fish caught in shallow water carry the greatest risk of contamination. Affected fish can not be identified by inspection, taste, smell or texture. Several non-specific methods for detecting contaminated fish are employed in Pacific island cultures, such as rubbing the fish liver on the gums or tasting the slime of the fish's eye. If a tingling sensation occurs, the fish is considered toxic. Others feed the fish to domestic animals and observe how they react.

Ciguatoxin is one of the most potent toxins known, with an LD_{50} estimated at 20 ng/kg.[4] Ciguatoxin is a heat-stable, lipid-soluble polyether that is not inactivated by cooking, freezing, drying, salting, smoking or marinating.[5] The toxin opens and prolongs the activated state of voltage-gated sodium channels in cell membranes. In neural tissue, this increase in sodium permeability results in a prolonged refractory period and a supernormal period of excitability.[4]