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Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals, October 2009

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Update on H1N1 Influenza

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On June 11, 2009, the World Health Organization (WHO) declared the first influenza pandemic since 1968.[1] Originally known as the "swine flu" or novel H1N1, the influenza strain has now been renamed 2009 H1N1 (A/California/7/2009 (H1N1) virus). The exact origins of the new strain remain unknown. However, the first clinical documentation of infection in humans occurred in Mexico in March 2009. The strain most likely evolved during the 2008-2009 seasonal flu season, resulting from a triple reassortment. The new virus contains components from human, avian, and swine sources.[2] The virus is now widespread throughout the Americas and has extended to parts of Europe and Asia.[3]

Transmission and incubation times appear to be similar to seasonal influenza. 2009 H1N1 is most likely transmitted through respiratory droplets. However, viral shedding in feces has been reported, suggesting a possible fecal-oral transmission. The incubation time appears to range from 2 to 7 days, similar to seasonal influenza. Viral shedding most likely begins 1 day prior to symptom development and may last up to 7 days after symptom onset or until symptoms dissipate. Children, and severely ill/immunocompromised patients may shed virus for longer periods of time.[2]

The virulence of 2009 H1N1 appears to be less than the Spanish influenza pandemic of 1918-1919, but similar to the Asian influenza pandemic of 1957 that killed approximately 2 to 4 million people worldwide. The estimated case fatality ratio is 0.4% with a range of 0.3-1.5% based on current reports. Based on the suspected infection rate, deaths could range from 6 to 12 million worldwide.[2] As of September 27, 2009 there have been more than 340,000 laboratory confirmed cases and over 4100 deaths reported to WHO.[3] Additionally, since that time, 99% of circulated influenza virus in the United States has been 2009 H1N1.[4]

Clinical Features

The clinical symptoms of 2009 H1N1 appear to be similar to seasonal influenza, with the most common symptoms including fever, sore throat, cough, malaise, headache, vomiting, and diarrhea. The majority of patients infected experience a mild course and typically recover in about 1 week without medical intervention. However, patients may experience severe complications, including lower respiratory tract infection, respiratory distress, secondary bacterial infections, and possibly death. Populations at high risk for complications from infection are listed in Table 1. In addition to these at risk populations, obesity appears to be a risk factor for severe disease. Seventy percent

(70%) of patients hospitalized with 2009 H1N1 possessed an underlying risk factor. The risk of hospitalization is greatest in children under 2 years of age.[2,4]

Early immunization reports suggest patients previously vaccinated repeatedly for seasonal influenza and patients older than 50 years old may have preexisting antibodies to 2009 H1N1 influenza. These antibodies are most likely due to cross-reactivity with previous seasonal influenza strains and exposure to H1N1 circulating prior to 1957.[1]

Diagnosis and Testing

Clinical symptoms and suspicion of influenza should drive diagnosis and treatment. However, multiple tests are available for testing influenza with varying degrees of sensitivity and specificity for 2009 H1N1.[5] Currently, the Center for Disease Control and Prevention (CDC) recommends that diagnostic testing be prioritized for hospitalized patients with suspected influenza and in patients for whom a diagnosis of influenza will change treatment, infection control measures or management of contacts. For patients with mild symptoms of influenza, diagnostic testing is not recommended.[5,6]

Several influenza diagnostic tests are available and include rapid influenza diagnostic tests (RIDTs), direct immunofluorescence assays (DFAs), real-time reverse transcriptase polymerase chain reaction (rRT-PCR), and viral culture. RIDTs are widely available and can detect influenza virus in 30 minutes or less. However, the sensitivity of these tests for 2009 H1N1 varies from 10 to 70%. Sensitivity of the RIDTs used at MUSC is estimated at 30%. However, the specificity of RIDTs is greater than 95%. Therefore, a negative RIDT does not exclude influenza infection, but a positive RIDT is highly suspicious of an acute infection. DFAs can yield results in 2 to 4 hours and have sensitivities for 2009 H1N1 ranging from 47 to 93% and specificities greater than 96%. Viral cultures are highly sensitive and specific. However, results of viral culture are often not provided in time to aid in clinical management but are important for public health surveillance. rRT-PCR is the most sensitive and specific diagnostic test for 2009 H1N1, with results typically being available in 1 to 2 days.[5,6]

According to the MUSC Microbiology Lab, the rRT-PCR will be available in October or November. Results will be reported as A:H1 seasonal flu, A:H3 seasonal flu, or A:nontypeable. A:nontypeable corresponds to 2009 H1N1 influenza. If a patient has an unusual presentation or dies, isolates will be sent to the Department of Health and Environmental Control (DHEC) for confirmation.

Treatment

Most patients infected with 2009 H1N1 experience uncomplicated illness and do not require antiviral therapy or hospitalization. Supportive care in these patients involves antipyretic use and fluid rehydration. Salicylates should not be used in patients under the age of 18 due to the risk of Reye's syndrome.[4,7]

However, for patients with severe infection or in patients at high risk for complications, antiviral therapy and hospitalization may be warranted. Supplemental oxygen should be given if hypoxemia occurs with goal oxygen saturations greater than 90% or possibly higher in certain clinical situations, including pregnancy. Antibiotic therapy should not be used unless concern for bacterial pneumonia exists. If bacterial pneumonia is suspected, treatment should follow community or hospital-acquired pneumonia guidelines.[7]

As of September 2009, 99% of circulating 2009 H1N1 virus was susceptible to both oseltamivir and zanamivir, but resistant to rimantadine and amantadine. Oseltamivir resistance is high among seasonal H1N1 influenza. However, since April 2009, seasonal H1N1 infections have been few in comparison with 2009 H1N1 in the United States. Therefore, CDC recommends treatment with either oseltamivir or zanamivir. If seasonal H1N1 becomes more prominent,

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treatment with zanamivir or a combination of oseltamivir and rimantidine or amantidine may be warranted.[4]

CDC recommends treatment for all hospitalized patients with confirmed, probable or suspected 2009 H1N1 or seasonal influenza. Treatment should be initiated as quickly as possible if influenza infection is suspected. Antivirals have been shown to be most effective if initiated within the first 48 hours of symptom onset and may decrease mortality and hospital duration. CDC recommends treating for 5 days. However, longer treatment may be warranted for patients with severe infections. Some experts have recommended using higher doses for severe illness although no data exists to prove increased effectiveness. FDA recently authorized an Emergency Use Authorization (EUA) for the use of oseltamivir in children under the age of 1 year. Both age-based and weight-based dosing have been advocated for this patient population and are included in Table 2. The recommended dosing for older children and adults are included in Table 3.[4]

Prevention

Standard infection control measures should be implemented for hospitalized patients with confirmed or suspected 2009 H1N1 infection. Patients should be placed on droplet precautions and proper hand hygiene should be followed.[2,7] CDC recommends against the standard use of antiviral chemoprophylaxis. However, chemoprophylaxis can be considered in patients at high risk for complications with exposure to a close contact with confirmed or suspected 2009 H1N1 or for health care personnel with unprotected exposure to 2009 H1N1. For antiviral chemoprophylaxis, oseltamivir or zanamivir is recommended. However, the few reported cases of 2009 H1N1 strains found to be resistant to oseltamivir typically developed in patients who became ill after receiving chemoprophylaxis, oseltamivir or zanamivir is recommended. However, the few reported cases of 2009 H1N1 strains found to be resistant to oseltamivir typically developed in patients who became ill after receiving chemoprophylaxis with oseltamivir. Because of the risk for resistance development, the use of early treatment is an alternative to chemoprophylaxis after a suspected exposure.[4]

Vaccinations have been recently developed and approved by FDA. Originally, it was believed two doses of the vaccine would be required due to the lack of previous exposure. However, the preliminary reports of a recent vaccine study in healthy adults aged 18 to 64 showed a profound immunogenic response to 1 dose of a monovalent, inactivated vaccine.[1] These results are promising, but further studies are needed to determine safety and efficacy in children and adults with underlying medical problems. Additionally, there is some new information from Sanofi-Pasteur, a manufacturer of the H1N1 vaccine, that suggest that children under the age of 10 may need 2 injections of the vaccine to get full protection.[8] The ability of vaccine production to meet the demands for both pediatric and adult immunizations remains an immense obstacle to universal vaccination.[9]

Conclusion

2009 H1N1 influenza poses a new threat to the world of healthcare. However, many aspects of the strain are similar to seasonal influenza. Through judicious infection control measures, appropriate antiviral usage, and a massive vaccination program, extensive morbidity and mortality can be avoided. A multidisciplinary effort is needed to ensure both patient and employee well-being. *(see page 4 for tables)*

Preliminary Data Show that Asthma Leads H1N1 Hospitalization Risk

October 15, 2009: Preliminary data from a CDC survey of patients hospitalized with 2009 H1N1 influenza virus infection have revealed that those with asthma and other underlying health conditions are at an increased risk for serious complications from the flu.

In adults, the most common underlying conditions associated with hospitalization were asthma and chronic lung disease. Twenty-six percent (26%) of the adults who were hospitalized had asthma. Ten percent (10%) had diabetes, 8% had other chronic lung disease besides asthma, 7.6% had immunosuppressive conditions, and 6.1% were pregnant.

Approximately 55% of adults hospitalized had at least 1 comorbid condition that may have worsened their flu course. Surveillance data came from CDC surveillance "hotspots." Information was compiled from 1400 adults and more than 500 children in 10 states who were hospitalized between April 2009 and the end of August.

According to preliminary data in hospitalized children, many of those patients had asthma, other chronic lung disease, neurological or neuromuscular diseases, sickle cell anemia, or other blood disorders.

CDC is still analyzing the data and has not yet classified risks for very young children, those who may be at high risk for complications from the flu, or very obese people who may be more at risk.

Table 1: Populations at Risk for 2009 H1N1 Complications

- Children younger than 2 years old
- Persons aged 65 years or older
- Pregnant women
- Persons of any age with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes)
- Immunocompromised patients
- Patients younger than 19 years of age who are receiving long-term aspirin therapy

Table 2: Oseltamivir Dosing Recommendations for Children < 1 Year of Age

Age-Based	Treatment Dose for 5 Days	Prophylaxis Dose for 10 Days
< 3 months	12 mg PO twice daily	Not recommended unless critical situation
3 to 5 months	20 mg PO twice daily	20 mg PO once daily
6 to 11 months	25 mg PO twice daily	25 mg PO once daily
Weight-Based	**Treatment Dose for 5 Days**	**Prophylaxis Dose for 10 Days**
≥ 9 months	3.5 mg/kg/dose PO twice daily	3.5 mg/kg PO once daily
< 9 months	3.0 mg/kg/dose PO twice daily	3.0 mg/kg PO once daily

Table 3: Antiviral Dosing Recommendations for Adults/Children > 1 Year of Age

Medication	Treatment (5 Days)	Chemoprophylaxis (10 Days)
Oseltamivir		
Adults		
	75 mg PO twice daily	75 mg PO once daily
Children ≥ 12 months		
≤ 15 kg	30 mg PO twice daily	30 mg PO once daily
>15 kg to 23 kg	45 mg PO twice daily	45 mg PO once daily
>23 kg to 40 kg	60 mg PO twice daily	60 mg PO once daily
> 40 kg	75 mg PO twice daily	75 mg PO once daily
Zanamivir		
Adults		
	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily
Children (≥ 7 years for treatment, ≥ 5 years for chemoprophylaxis)		
	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily

Update: MUSC Influenza Vaccine Shortage

The ordered amount of seasonal influenza vaccine was significantly reduced due to various factors. Therefore, the original plans to provide vaccine to all patients and employees wishing to be vaccinated has been adjusted.

Ambulatory Patients: For patients scheduled in MUSC-MC clinics the following populations are eligible for influenza vaccination. If a patient does NOT meet the below criteria, please encourage them to receive their vaccine elsewhere:

- Women who will be **pregnant** during influenza season.
- Anyone with a **weakened immune system** due to: HIV/AIDS or other diseases affecting the immune system; long-term treatment with drugs such as steroids; cancer treatment with x-rays or drugs
- Anyone with certain **muscle or nerve disorders** (such as seizure disorders or cerebral palsy) that can lead to breathing or swallowing problems.
- Anyone 6 months through 18 years of age on **long-term aspirin treatment** (they could develop Reye Syndrome if they got influenza).
- Anyone with **long-term health problems** with: heart disease; kidney disease; liver disease; lung disease; metabolic disease, such as diabetes; asthma; anemia, and other blood disorders

Inpatients: All inpatients should be screened for seasonal flu vaccine. The inpatient order form is being modified to take into account the previously mentioned high-priority patients. A portion of our flu vaccine has been reserved for them.

Staff: Out of the current supply, we have allocated as much vaccine as possible for staff, while still meeting patient needs. Hospital Leadership is determining the priority groups and the timeline for vaccination based on patient populations served and providers critical to the operations of the hospital. We encourage staff who wish to obtain the seasonal influenza vaccine sooner to visit their Primary Care Physician or local pharmacy (see page 6).

All employee tent events for October have been cancelled. We are working with our distributors and manufacturers to obtain more vaccine. If adequate future shipments are received, employee events will be rescheduled.

*Did You Know…*New USP Standards for Heparin Products Will Result in Decreased Potency (FDA Alert):

To ensure the quality of heparin and to guard against potential contamination, the United States Pharmacopoeia (USP), a nonprofit standards-setting organization, adopted new manufacturing controls for heparin. These changes include a modification of the reference standard for the drug's unit dose.

Manufacturers in the United States label the amount of heparin included in their products based on USP standards. The changes adopted by the USP for the heparin unit dose match the World Health Organization's International Standard (IS) unit dose definition that has been in use in Europe for many years. The revised USP reference standard and unit definition for heparin is about 10% less potent than the former USP unit.

Manufacturers for the U.S. market have begun to make heparin using the new USP standard. While the USP manufacturing controls take effect Oct. 1 for production, the FDA has asked that they not ship this new product to customers until Oct. 8, 2009, or later. The delay will give health care providers and facilities time to learn about the changes and to make adjustments to their pharmacy procedures and dosing practices. Four companies market heparin in the United States: APP, the largest manufacturer, markets heparin in vials; Hospira markets heparin in intravenous bags, vials, and syringes; Baxter markets heparin in intravenous bags; and B. Braun markets heparin in intravenous bags. The FDA has asked that all manufacturers identify their new products to help pharmacies and health care professionals differentiate them from the former products.

At this time it is believed that subcutaneous dosing will not be clinically affected For treatment bolus and continuous infusions, increased monitoring may be required. The Department of Pharmacy Services will be monitoring this heparin issue closely. Guidelines and recommendations will be developed and disseminated in the near future.

FDA Alert to Health Care Professionals: http://www.fda.gov//Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm184502.htm

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CVS	www.cvs.com **1-888-FLU SHOT** *Call or go to the web-site for more dates and locations*	**Monday, 10/19/2009** 10:00 AM - 02:00 PM 640 Long Point Rd., Mt. Pleasant Phone: 843-881-5644 **Wednesday, 10/21/2009** 10:00 AM - 02:00 PM **1)** 10599 Dorchester Rd., Summerville (Intersection of Highway 61) Phone: 843-871-7701 **2)** 431 St. James Ave., Goose Creek Phone: 843-572-2606	$35.00
Walgreen's	www.walgreens.com *Call individual store for Most are offering shots everyday.*	**Everyday** 10:00 AM – 4:00 PM 1810 Hwy 17 - North (US Hwy 17 & James Nelson), Mount Pleasant Phone: 843-388-2585	$24.99 (regular flu shot) $29.99 (thimerosal/ mercury-free flu shots) $29.99 (Live attenuated flu vaccine nasal spray)
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FORMULARY UPDATE FOR SEPTEMBER 2009

In September 2009, the Pharmacy and Therapeutics Committee approved the actions listed below. The formulary effective date was October 15, 2009.

ADDED WITH RESTRICTION

Clevidipine (Cleviprex®)

Clevidipine is a new dihydropyridine IV calcium channel blocker that is short-acting and vasoselective. It was added to the formulary with restrictions to the critical care areas (ie, ICUs, ORs, ED) and the Interventional Radiology area (must be monitored by Anesthesia). Safety concerns with clevidipine include its contraindications in patients with soy or egg-allergies. Since the product contains lipids, the bottle must be changed every 4 hours to avoid microbial growth.

200-mg/20-mL vials

ADDED

Esomeprazole (Nexium®)

Esomeprazole was determined to be an effective alternative to other available proton pump inhibitors (PPI) and added to the formulary as the primary PPI for all patient populations (ie, adult, pediatric, neonate). Therefore, all other PPIs (pantoprazole, omeprazole**, and lansoprazole) will be removed from the formulary.

*** Except for extemporaneous suspension (for use in pts < 10 kg)*

20- and 40-mg capsules; 10-, 20-, and 40-mg oral suspension packets; 20-and 40-mg vials

TO REMAIN ON FORMULARY:

Omeprazole (Prilosec®) extemporaneous suspension

Until extended stability data can be obtained for esomeprazole suspension, omeprazole suspension will be available for patients less than 10 kg.

2-mg/mL extemporaneous suspension

CHANGE IN RESTRICTION

Buprenorphine/Naloxone (Suboxone®)

Due to the federal requirements for initiation of opioid-dependence treatment, the ordering of buprenorphine/naloxone was restricted to physicians authorized by the Substance Abuse and Mental Health Services Administration. However, in patients stabilized on treatment and admitted to the hospital for other reasons, the federal restrictions do not apply. Therefore, the restriction will now state that prescribing be limited to the following:

- *IOP physicians initiating/ maintaining treatment for opioid dependence:* must be authorized by the Substance Abuse and Mental Health Services Administration.
- *Patients that are stabilized on maintenance treatment and are admitted to a non-IOP service*: any inpatient provider may prescribe; however, treatment and dose should be verified with the outpatient provider.

NOT ADDED

Methylnaltrexone (Relistor®)

Methylnaltrexone is a peripherally-acting mu-opioid receptor antagonist that acts in the gastrointestinal tract. Methylnaltrexone has shown efficacy at providing relief from opioid induced constipation in patients suffering from advanced illness in palliative care settings. It has not been evaluated for efficacy and safety in any other patient populations. The medication has minimal safety concerns, as it has been demonstrated to have a mild side effect profile. Methylnaltrexone is considered a last-line therapy in patients with advanced illness and suffering from opioid-induced constipation unresponsive to stool softeners or stimulant laxatives, mainly due to its prohibitive costs.

LINE EXTENSIONS

- Amylase/lipase/protease (Creon®) 6,000- 12,000-, and 24,000-unit capsules

DELETIONS

- Amylase/lipase/protease(Creon®): 5000-, 10,000-, and 20,000-unit capsules
- Ondansetron (Zofran®) 24-mg tablets
- Carnation Good Start
  - Formula for the Level 1 Nursery will return to the previous method of alternating the Ross and Mead Johnson products.

CHARTS, GUIDELINES, AND ORDER FORMS

Metformin Order Entry Hard Stop

Based on recommendations from the Institute for Safe Medication Practices (ISMP) visit, the Pharmacy Practice Committee has developed an order entry hard stop for metformin. This stop will not allow the pharmacist to enter any metformin order on patients with an elevated serum creatinine concentration (≥ 1.4 mg/dL – females; ≥ 1.5 mg/dL – males). Details and education will be provided prior to the implementation date (TBD).

Intravenous to Oral Automatic Conversion Program

Pre-printed stickers will be placed in the orders and progress notes sections of the patient chart when a patient and medication meet pre-specified inclusion criteria in the protocol. Prescribers are given the option to not participate in this program for any given order. Critically ill patients in the ICUs will not be eligible for this program. The policy and protocol requires Medical Executive Committee approval.