

CDPH Health Advisory Severe Influenza Update – January 3, 2014

As you may know, there have been recent reports of critically ill children and young and middle aged adults with complications associated with influenza (including healthcare-associated influenza) at several centers in the U.S., including in California. To date, four influenza-associated deaths in persons under age 64 years old have been reported in California; none of the fatal cases were children. In addition, we have received a number of reports of critically ill influenza patients with ARDS in intensive care units; most of these patients have been young or middle aged adults.

The predominant influenza virus this season to date is influenza A(H1N1)pdm09 virus. This is the same virus that caused the 2009 H1N1 pandemic and it has not changed much antigenically to date, although antigenic drift is expected. As noted, some hospitals are reporting cases of non-elderly adults with critical illness due to influenza A (H1N1)pdm09 virus, similar to the epidemiology observed during the 2009 pandemic. Although it is early in the influenza season, influenza activity is expected to increase substantially in the coming weeks to months. Therefore, primary prevention with influenza vaccination is strongly recommended – all persons aged 6 months and older, including healthcare personnel should receive influenza vaccination now.

The information in this email is intended for clinicians caring for influenza patients, particularly severely ill patients. It is also useful for clinicians to communicate with local and state public health colleagues about influenza patients and influenza testing, especially regarding patients with severe and fatal outcomes.

Some information for consideration regarding clinical management of hospitalized patients with suspected or confirmed influenza this season is provided below. While this information is consistent with CDC recommendations, it is not meant to represent official recommendations from CDPH or CDC. Feel free to share this information with colleagues who are involved in clinical management of influenza patients. For updated information on influenza activity, influenza vaccines, and other recommendations, clinicians can view the CDC influenza webpages at: <http://www.cdc.gov/flu/>

High-risk persons and influenza complications

- 1) Persons at high-risk for influenza complications include infants and young children aged <2 years, pregnant women, elderly persons, persons of any age with certain chronic co-morbidities (cardiac: coronary artery disease, CHF [but not HTN alone]; pulmonary; COPD, asthma; renal disease; hematologic disorders; metabolic disorders; neurologic and neuromuscular disorders; immunocompromised/immunosuppression; morbid obesity; nursing home residents; American Indian/Alaska Native). However, otherwise healthy non high-risk persons can also experience severe and fatal complications associated with influenza, especially with influenza A(H1N1)pdm09 virus infection.
- 2) Clinical complications associated with influenza include exacerbation of underlying chronic disease, viral pneumonitis/pneumonia/respiratory failure/ARDS and croup/bronchiolitis in infants, bronchospasm, secondary bacterial pneumonia, encephalopathy/encephalitis; myocarditis/pericarditis; myositis/rhabdomyolysis; etc.

Influenza treatment

- 1) Empiric antiviral treatment with oral/enteric oseltamivir should be started ASAP on any hospitalized patient with suspected influenza. There is no need to wait for influenza testing results – the greatest clinical benefit is when antiviral treatment is started as soon as possible, ideally closest to illness onset. However, observational studies indicate the clinical benefit of reducing complications and increasing survival even when antiviral treatment is started late. For high-risk outpatients and persons with progressive disease who are not being admitted, antiviral treatment is also recommended as soon as possible.
- 2) Oral/enteric oseltamivir treatment duration is five days; consider longer duration for critically ill patients.
 - a) Critically ill patients with influenza may be treated with higher doses of oseltamivir (e.g., 150 mg orally every 12 hours for 10 days in patients with normal renal function). Limited data indicate that administering oseltamivir via a gastric tube can provide systemic absorption in some critically ill patients.
 - b) Gastric stasis or bleeding can make the gastric tube administration route problematic because of the potential for reduced absorption of medication. For these patients, parenteral medications might be preferable, but no clinical trials have demonstrated increased benefit, and none are FDA-approved, although an intravenous formulation of zanamivir is available under an emergency investigational new drug (EIND) protocol (see below).
- 3) If patients continue to do poorly on oral oseltamivir or have gastric stasis or bleeding, use of intravenous zanamivir may be considered. IV zanamivir is an investigational drug that is chemically similar to oseltamivir and is available for compassionate use through the manufacturer GSK, and by urgent EIND approval by the Food and Drug Administration.
 - a) To make an EIND request for IV zanamivir, contact: 301-796-1500 (8:00AM - 4:30PM EST). After business hours (4:30 pm – 8:00 am EST): call the FDA Emergency Coordinator at 866-300-4374 or 301-796-8240 or call the CDER Emergency Coordinator at 301-796-9900.
 - b) Dosage adjustment for IV zanamivir may be indicated for patients requiring renal replacement therapy or who are on ECMO.
 - c) GSK is conducting an IV zanamivir clinical trial at two sites in California: Chula Vista and La Mesa. For Chula Vista call 619-955-5246 and for La Mesa call 619-567-1550. For more information see: <http://tinyurl.com/m2jpp3k>
 - d) Patients with respiratory failure can have prolonged influenza viral replication in the lower respiratory tract (weeks), and immunocompromised patients can shed influenza viruses for weeks to months. Therefore, there is a risk for emergence of oseltamivir resistance. IV zanamivir can treat oseltamivir-resistant influenza A(H1N1)pdm09 virus infection.
- 4) Do not expect rapid clinical improvement once antiviral treatment is started, the main pathogenesis is cytokine dysregulation, but reducing influenza viral load in the respiratory tract may be helpful. Other complications associated with influenza in a patient with respiratory failure include vasopressor-dependent shock, and renal failure.
- 5) Avoid high-dose systemic corticosteroids for treatment of influenza except for patients on chronic treatment when treating the underlying chronic disease exacerbation (e.g., COPD, asthma exacerbation) because high-dose corticosteroids may prolong influenza viral shedding and increase the risk for VAP and death. However, low-dose hydrocortisone is okay in influenza patients with suspected/documentated adrenal insufficiency or refractory septic shock.

- 6) CDPH has recently received requests for the unapproved antiviral drug peramivir IV to treat hospitalized patients with influenza. During H1N1, peramivir was potentially available under an FDA issued Emergency Use Authorization (EUA) on a case by case basis when requested by a treating physician for a particular hospitalized patient. The EUA for distribution and use of peramivir expired on June 23, 2010. According to CDC guidance, any leftover or unused peramivir is to be destroyed and not kept for future use. Peramivir is currently not available from either the CDC or from the manufacturer.
- 5) For patients who are intubated, use of the zanamivir disc inhaler is not possible. Suboptimal delivery to sites of infection in patients with pneumonic or extrapulmonary disease is of concern for patients with severe respiratory illness. Use of the nebulized preparation of the licensed powder formulation contained in the disc inhaler is not recommended because it has been demonstrated to clog ventilator tubing.

Testing

- 1) Collect both upper and lower respiratory tract specimens for influenza testing in hospitalized patients with suspected influenza - if ventilated, endotracheal aspirate specimens should be sent unless a BAL is done for other diagnostic reasons (lower respiratory tract specimens can yield the diagnosis when influenza viral shedding is no longer detectable in the upper respiratory tract, therefore negative influenza testing results on an upper respiratory tract specimen in a critically ill patient with lower respiratory tract disease does not exclude influenza).
- 2) For influenza testing, RT-PCR is recommended. There are approved molecular assays and also testing can be done at public health laboratories and academic medical centers; antigen detection tests such as rapid influenza diagnostic tests and immunofluorescence assays (DFA) lack sensitivity and false negative results are common so a negative result does not rule out influenza virus infection; repeat by RT-PCR assay if influenza is still suspected.
- 3) Patients receiving antiviral medications who do not respond to treatment might have an infection with an antiviral-resistant influenza virus. Oseltamivir resistance, sometimes within 1 week of treatment initiation, has been reported particularly among immunocompromised patients with 2009 H1N1 virus infection who were receiving treatment with oseltamivir. Oseltamivir resistance should be suspected in patients who are persistently positive with repeated PCR testing, particularly if they are immunocompromised. Specimens from these patients can be sent to the CDPH VRDL and CDC for testing for antiviral resistance.
- 4) All specimens collected on critically ill or fatal cases with suspected or laboratory-confirmed influenza should be referred to a public health laboratory for further PCR confirmation and subtyping. The CDPH Viral and Rickettsial Disease Laboratory is also available for surge capacity testing as needed.

Infection Control

Infection prevention and control for influenza is an essential part of clinical management for influenza patients, including prevention of healthcare-associated influenza. Cases of critically ill patients with healthcare-associated influenza have already been reported in the U.S. this season.

- All healthcare personnel should receive influenza vaccination this season.
- Droplet precautions, in addition to Standard precautions, should be implemented for the routine care of influenza patients.

- Influenza patients should be isolated in a single room or cohorted with other influenza patients if single rooms are not available.
- For aerosol-generating procedures, healthcare personnel should use an N95 respirator or higher level of respiratory protection and the procedure should be done in an airborne infection isolation room, if possible.
- Influenza prevention should be strengthened throughout the hospital, including the ER, ward, and ICU, with active daily surveillance for nosocomial influenza (new fevers and new respiratory symptoms in hospitalized patients).
- Ill healthcare personnel should be excluded from work.
- Visitors should be screened for illness, if feasible. Visitors to patients in isolation for influenza should be limited to persons who are necessary for the patient's emotional well-being and care. Visitors who have been in contact with the patient before and during hospitalization are a possible source of influenza for other patients, visitors, and staff. Some hospitals do not allow young children to visit during influenza/RSV season.
- Take steps to ensure all persons with symptoms of a respiratory infection adhere to respiratory hygiene, cough etiquette, hand hygiene, and triage procedures throughout the duration of their visit, including providing facemasks to such persons.
- For more information on influenza infection control, see: <http://tinyurl.com/3m6b7od> and <http://tinyurl.com/242awwf>

Reporting

- Hospitals: Laboratory-confirmed fatal influenza cases <65 years of age are reportable in California. In addition, laboratory-confirmed influenza cases requiring intensive care are voluntarily reportable and some local health jurisdictions have asked that hospitals report these cases. Because of the concern about severe cases this season, CDPH is requesting that all hospitals report ICU cases to their local public health department.
- Local health jurisdictions: LHJs are asked to report laboratory-confirmed influenza in cases requiring intensive care and fatal cases age 0-64 years promptly to CDPH. Cases should be reported using CalREDIE or faxing the "Severe Influenza Case History Form," which is available at: <http://tinyurl.com/p3nexvk> to 916-440-5984.