

To: UNC Health Care Physicians

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Re: Influenza: Update on Epidemiology, Diagnosis and Treatment

Key Points Regarding Influenza

- North Carolina has widespread influenza activity
- UNC McLendon laboratories provides three options for influenza testing, including a rapid PCR test for the Emergency Department and select clinic locations (see below for details)
- UNC Health Care has developed a comprehensive set of age/weight based recommendations for the dosing of neuraminidase inhibitors (see below for details). UNC Health Care has access to 3 IRB/FDA approved protocols for IV neuraminidase inhibitors for hospitalized patients unable to take or tolerate oral/inhaled antivirals.
- Patients at “high-risk” for the complications of influenza should have appropriate a lab test obtained for diagnosis and receive treatment (see below for a complete list of “high-risk” conditions).

North Carolina has been experienced widespread influenza activity since mid-December with a dramatic increase in the past 10 days. To date UNC McLendon Laboratories has identified 61 isolates of influenza of which more than half have been type B. Two deaths from viral influenza have been reported in the State.

The Clinical Microbiology-Immunology Laboratory currently has three options for influenza testing; the characteristics of each are outlined below. Rapid antigen testing and viral culture are no longer offered. Due to the decrease in sensitivity for the detection of H1N1 (2009) influenza A virus relative to our traditional influenza A/B PCR (performed 2X/day M-F; 1X/day weekends), the “rapid” PCR test will be reserved for the Emergency Department and select clinic locations on an as-needed basis.

Test Name (SMS)	Influenza A and B Detected	Influenza A Typing	Other* Respiratory Viruses Detected	Acceptable Specimens	Sensitivity	Specificity	Turn-around-time	Testing Schedule
Rapid Influenza PCR	Yes	H1N1 (2009) only	No	NP swab NP aspirate	A/H1N1 (2009): 80% A/Seasonal H1: 99-100% A/H3: 99-100% B: 99-100%	100%	90 min	24/7
Influenza Virus, PCR	Yes	No	No	Upper and lower respiratory	Reference method	Reference method	24 hours (max)	Daily [†]
Respiratory Virus Group, NAA	Yes	Seasonal H1 and H3 only	Yes*	Upper and lower respiratory	A: 93-96% B: 99-100%	96-100%	24-96 hours	M-F [‡]

*Other viruses detected include: respiratory syncytial virus, parainfluenza 1/2/3, metapneumovirus, rhinovirus/enterovirus, and adenovirus (50% sensitivity).

[†]Currently, 2 runs per day M-F, and one run per weekend day. See website for updates to testing schedule as the respiratory season progresses: http://labs.unchealthcare.org/labstestinfo/i_tests/influenza_pcr.htm

[‡]See website for reporting schedule based on time received into the laboratory: http://labs.unchealthcare.org/labstestinfo/r_tests/rpv_naa.htm

The sensitivity and specificity data presented above were determined using the Influenza A/B PCR as the gold standard. Sensitivity is dependent on the stage of the illness (<5 days most sensitive) and the proper collection of the nasopharyngeal swab. For a demonstration of proper collection technique please review the NEJM video at: <http://www.youtube.com/watch?v=DVJNWefmHjE> A nasopharyngeal swab is the specimen of choice for acute upper respiratory tract infection and should be transported to the laboratory as soon as possible in universal transport media (UTM). For off-campus locations, swabs in UTM should be refrigerated until delivery to the laboratory. Details for ordering NP swabs with UTM can be found here: http://labs.unchealthcare.org/forms/naso_wall_chart.pdf. For more information, consult the McLendon Clinical Laboratories website at <http://labs.unchealthcare.org/> or contact Dr. Melissa Miller at pager 216-6131.

The CDC recommends antiviral treatment as early as possible for any patient with confirmed or suspected influenza in the following groups (testing for influenza virus should strongly be considered in the same groups):

- Has severe, complicated, or progressive illness, or
- Is hospitalized, or
- Is at higher risk for influenza complications as follows:
 - Children <2 years of age
 - Adults 65 years or older
 - Persons with the following conditions:
 - Chronic pulmonary (including asthma),
 - Cardiovascular (except hypertension),
 - Renal,
 - Hepatic,
 - Hematologic (including sickle cell disease),
 - Neurological and neurodevelopment conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury],
 - Metabolic disorders (including diabetes mellitus)
 - Persons with immunosuppression, including that caused by medications or by HIV infection;
 - Women who are pregnant or post-partum (within 2 weeks after delivery);
 - Persons younger than 19 years of age who are receiving long-term aspirin therapy;
 - American Indians
 - Persons who are morbidly obese (body-mass index ≥ 40);
 - Residents of nursing homes and other chronic-care facilities

Neuraminidase inhibitors such as zanamivir (Relenza) and oseltamivir (Tamiflu) are the drugs of choice for prophylaxis or treatment of viral influenza. They can be used for seasonal prophylaxis, post-exposure prophylaxis or treatment. Treatment with neuraminidase inhibitors has been demonstrated to reduce the duration of illness, decrease the risk of hospitalization in "high-risk" patients, and decrease the risk of death in hospitalized patients. UNC Health Care has developed a comprehensive guide to age/weight based dosing including for neonates and young children (see attached):

For hospitalized patients unable to tolerate oral/inhaled medications UNC Hospitals has three IRB/FDA approved studies of IV neuraminidase inhibitors. Please contact Megan Avots RN (216-6450) or Christopher Hurt MD (216-2167) to enroll patients.

Agent, Age group		Treatment (5 days*)	Chemoprophylaxis (10 days)
ORAL ANTIVIRAL THERAPY			
Oseltamivir (Tamiflu): Preferred drug for all INPATIENTS or any patients under 5-7 years of age			
Adults		75 mg capsule twice daily	75 mg capsule once per day
Children ≥ 12 months AND ≥ 10 kg	15 kg or less	30 mg twice daily	30 mg once per day
	16-23 kg	45 mg twice daily	45 mg once per day
	24-40 kg	60 mg twice daily	60 mg once per day
	>40 kg	75 mg twice daily	75 mg once per day
Children < 12 months OR < 10 kg	< 1 week of age	2 mg/kg/dose once daily	
	≥ 1 week to < 3 months	2 mg/kg/dose twice daily Max 12 mg twice daily	Not recommended unless situation judged critical due to limited data in this age group
	3 - 5 months	2.5 to 3 mg/kg/dose twice daily Max 20 mg twice daily	2.5 to 3 mg/kg/dose once daily Max 20 mg once daily
	6 - 8 months	2.5 to 3 mg/kg/dose twice daily Max 25 mg twice daily	2.5 - 3 mg/kg/day once daily Max 25 mg once daily
	9 - 11 months	3 to 3.5 mg/kg/dose twice daily Max 30 mg twice daily	3 - 3.5 mg/kg/dose once daily Max 30 mg once daily
ORAL ANTIVIRAL THERAPY			
Zanamivir (Relenza): Preferred** drug for all OUTPATIENTS unless pre-existing airway disease (e.g., asthma) due to risk of bronchospasm or if patient is under 5-7 years of age			
Adults		Two 5-mg inhalations (10 mg total) twice per day	Two 5-mg inhalations (10 mg total) once per day
Children		<7 years Use oseltamivir	<5 years: Use oseltamivir
		≥7 years: Two 5-mg inhalations (10 mg total) twice per day	≥5 years: Two 5-mg inhalations (10 mg total) once per day (age, 5 years or older)
IV ANTIVIRAL THERAPY			
IV neuraminidase inhibitors are available under IRB protocols. The main contacts for influenza studies are: Megan Avots, RN (pager 216-6450) and Christopher Hurt, MD (pager 216-2167).			

*If patient is admitted to an ICU, then consider extending therapy duration to 10 days in total.

**Both zanamivir (Relenza) and oseltamivir (Tamiflu) are acceptable for outpatient treatment or prophylaxis. Preferential use of Relenza in outpatients will help maintain availability of Tamiflu for pediatric patients, patients with airway disease, and inpatients.

Dosing adjustment in renal impairment: *Oseltamivir*. For CrCL < 30 mL/min or GFR 10-30% of normal, adjust dosing frequency to once daily for treatment or once every other day for prophylaxis. Avoid use in renal failure.

Zanamivir. No dose adjustment is needed in renal impairment.

Dosing adjustment in hepatic impairment: None needed for either drug if mild to moderate hepatic impairment.

Product Information

Oseltamivir (Tamiflu) is available in 75 mg unit dose capsules and a 12 mg/mL; 25 mL bottle of oral suspension. If the suspension is in short supply, an oral suspension can be compounded from the capsules. Alternatively, the capsules can be opened and the drug can be mixed in some chocolate syrup, orange juice, or applesauce.

Zanamavir (Relenza) is available as a kit containing 1 inhaler and 5 disks. **Each dose is 2 inhalations.** Each of the disks contains 4 inhalations which equals 1 day of treatment or 2 days of prophylaxis. **The kit cannot be broken apart to dispense individual doses, so this is best for outpatient therapy.** One kit = 5 days of treatment or 10 days of prophylaxis. DO NOT use zanamivir in patients with pre-existing airway disease (e.g, asthma) due to the risk of bronchospasm.

SPECIAL POPULATIONS:

Infants Less Than 1 Year of Age

Monitoring: Apnea, hypoglycemia, renal function

The oral suspension contains sodium benzoate. This is not a contraindication for use in neonates. Benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates. Sodium benzoate can also displace bilirubin from protein-binding sites. Please note that the volume of drug will be small (i.e., the suspension concentration is 12 mg/mL) and the duration will be short (i.e., 5 days).

Some experts prefer weight-based dosing for children aged younger than 1 year, particularly for very young or premature infants based on preliminary data from a National Institutes of Health- funded Collaborative Antiviral Study Group (CASG). When using weight-based dosing for infants aged younger than 1 year for treatment, those 9 months or older should receive 3.5 mg/kg/dose BID, and those aged younger than 9 months should receive 3.0 mg/kg/dose BID. When using weight-based dosing for infants aged younger than 1 year for chemoprophylaxis, those 9 months or older should receive 3.5 mg/kg/dose QD, and those aged younger than 9 months should receive 3.0 mg/kg/dose QD (Source: D Kimberlin et al. *Oseltamivir (OST) and OST Carboxylate (CBX) Pharmacokinetics (PK) in Infants: Interim Results from a Multicenter Trial.* Abstract accepted to Infectious Diseases Society of America meeting, October 2009). Health care providers should be aware of the lack of data on safety and dosing when considering oseltamivir use in a seriously ill young infant with confirmed 2009 H1N1 influenza virus infection or who has been exposed to a confirmed 2009 H1N1 influenza case, and carefully monitor infants for adverse events when oseltamivir is used. Additional information on oseltamivir for this age group can be found at:

<http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM153547.pdf>  

Pregnant Women

Pregnant women are known to be at higher risk for complications from infection with seasonal influenza viruses, and severe disease among pregnant women was reported during past pandemics. Hospitalizations and deaths have been reported among pregnant women with 2009 H1N1 influenza virus infection, and one study estimated that the risk for hospitalization for 2009 H1N1 influenza was four times higher for pregnant women than for the general population. While oseltamivir and zanamivir are "Pregnancy Category C" medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women, the available risk-benefit data indicate pregnant women with suspected or confirmed influenza should receive prompt antiviral therapy. Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use. Because of its systemic activity, oseltamivir is preferred for treatment of pregnant women. The drug of choice for chemoprophylaxis is less clear. Zanamivir may be preferable because of its limited systemic absorption; however, respiratory complications that may be associated with zanamivir because of its inhaled route of administration need to be considered, especially in women at risk for respiratory problems.

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