INFLUENZA

INTRODUCTION (CARRIE DANZIGER, M.D. 10/2015)
Influenza virus (or flu) is a respiratory tract pathogen. Outbreaks of the influenza virus occur because the virus has a high propensity for antigenic change of the envelope glycoproteins (hemagglutinin and neuraminidase). These changes can be minor and lead to local epidemics (such as the annual seasonal outbreaks of the flu). They may also be major leading to the occurrence of worldwide pandemics. While minor outbreaks may occur every 2-3 years, pandemics are estimated to occur every 10-20 years. The most recent is the H1N1 pandemic of 2009.

Influenza has a high degree of transmissibility. It is transmitted via respiratory secretions (cough or sneeze) or via contaminated surfaces. Once infected, viral shedding peaks at 24-48 hours, and continues for 5-10 days.

Rates of serious illness and death are highest among children < 2yo, adults > 65yo, and those with underlying medical conditions. However, approximately half of pediatric deaths and 40-50% of admissions occur in those without high-risk medical conditions.

Influenza vaccination is targeted to the most likely strains predicted for the coming year. Mutation in the prior year strains and emergence of new strains can make vaccination less effective. Immunity after vaccination decreases approximately 50% within 6-12 months so annual vaccination is recommended.

CLINICAL PRESENTATION
Symptoms typically start 1-4 days after exposure as an acute, febrile respiratory illness. Patients' symptoms may include high fever, chills, malaise, headache, myalgias, fatigue, sore throat, nasal congestion, cough, and conjunctivitis. Younger children are more likely to have gastrointestinal tract symptoms including vomiting and diarrhea. Illness is usually mild and self-limited though it can lead to exacerbations of underlying chronic medical conditions as well as respiratory and non-respiratory complications.

CDC CASE DEFINITION
Influenza like illness (ILI) is defined as:

A documented fever (>100.4 F or > 38.0 C) with
Respiratory symptoms (cough OR sore throat)

INFLUENZA COMPLICATIONS	
Upper respiratory tract disease	Sinusitis, otitis media, croup
Lower respiratory tract disease	Bronchiolitis, pneumonia, asthma exacerbation
Cardiac disease	Myocarditis, pericarditis
Musculoskeletal disease	Myositis, rhabdomyolysis
Neurologic disease	Acute and post-infectious encephalopathy, encephalitis, febrile seizures, status epilepticus
Systemic disease	Post influenza staph toxic shock syndrome

	Secondary bacterial pneumonia, sepsis
CHILDREN AT RISK FOR INFLUENZA COMPLICATIONS: AAP/CDC 2015	
1	< 2 years of age or ≥ 65 years
2	Neurological disorders such as:
	Epilepsy or cerebral palsy
	Neuromuscular disorders (eg, muscular dystrophy, spinal cord injury)
	Moderate to severe developmental delay, mental retardation
3	Chronic respiratory diseases (including asthma)
4	Immunodeficiency/Immunosuppression
5	Chronic cardiac, metabolic, renal, hepatic, endocrine or hematologic disease
6	Long term aspirin therapy (< 19 years of age)
7	Residents of chronic care facilities and nursing homes
8	Pregnancy (including up until 2 weeks post partum)
9	Morbid obesity (BMI ≥ 40)
10	American Indians or Alaskan natives

LABORATORY TESTING

Rapid influenza diagnostic tests are known to have poor sensitivity (10-70%) but high specificities (71-83%). A negative rapid test does not rule out infection and should not be used to determine the need for treatment. Definitive testing is available using real time reverse transcriptase tests (rRT-PCR) or cell culture. A point of care rapid influenza PCR test (Roche) has been FDA approved (2015) but is not yet available.

INFLUENZA TESTING RECOMMENDATIONS: AAP
All patients being admitted with acute febrile respiratory illness
When testing will determine a change in management – Treatment with an antiviral or avoidance of testing to identify another etiology of infection
As a basis for additional infection control measures – eg Cohorting of admissions
A family member with high risk of influenza complications

MANAGEMENT: ANTIVIRAL MEDICATIONS

Two classes of medications are available for the treatment of influenza. The neuraminidase inhibiters (Oseltamivir or Zanamivir) interfere with the release of virus from the cell and are effective against all influenza strains. The amantadines (Amantadine and Ramantidine) interfere with viral uncoating inside the cell. They are effective against influenza A but not influenza B and are associated with more adverse effects. Recent high level of influenza A resistance have made the amantadines less effective. The neuramindase inhibitors are recommended for antiviral treatment of the currently circulating influenza strains.

There is considerable controversy regarding the indications for the use of antivirals. A 2014 Cochrane review, including previously unpublished studies, demonstrated a 16.8 hour reduction (from 7.0 – 6.3 days) in the duration of symptoms if antivirals are given within 48 hours of symptoms onset. There was no difference in influenza complications or admissions. Inclusion of subjects with unconfirmed influenza may have decreased the apparent efficacy of antivirals.

However, based on other studies that demonstrate efficacy in reducing complications, admissions and death the AAP, CDC, WHO and Infectious Disease Society of America recommend the use of antivirals in defined circumstances.

Potential downsides of therapy include: a cost of over $100 for an adult course of Oseltamivir, the potential for increasing antiviral resistance and common adverse events. These include nausea (number needed to harm = 28), headache (NNH = 32) and neuropsychiatric events (NNH = 94).

Neuropsychiatric events have been demonstrated primarily in Japanese children less than 16 years of ago and include: confusion, hallucinations, self-injurious behavior and seizures. The etiology of these neuropsychiatric events and the predilection for Japanese children are unknown. A link between Oseltamivir and neurologic or psychiatric events has not been established in surveillance studies.

ANTIVIRAL TREATMENT RECOMMENDATIONS: AAP 2015
Treatment should be <u>offered</u> as early as possible for: (regardless of influenza immunization status and whether the onset of illness has been less than 48 hours)
Any hospitalized child clinically presumed to have influenza disease or progressive illness attributable to influenza
Influenza infection of any severity in children at high risk of complications
Treatment should be <u>considered</u> for:
Any otherwise healthy child clinically presumed to have influenza disease for whom a decrease in duration of clinical symptoms is felt to we warranted. (The greatest effect on outcome will occur if treatment can be initiated within 48 hours of illness onset but still should be considered if later in the course of illness)
Children clinically presumed to have influenza disease and whose siblings either are younger than 6 months or have underlying medical conditions that predispose them to complications of influenza.

MEDICATION DOSING: AAP/CDC 2015		
Oseltamivir* (Tamiflu) 30, 45, 75 mg capsules, 6 mg/ml suspension		
Preterm Infants		See Table Below
Term Infants: 0-8 months		3.0 mg/kg/dose BID x 5 days
Infants: 9-11 months		3.5 mg/kg/dose BID x 5 days
Children ≥ 12 months	< 15 kg	30 mg BID x 5 days
	15-23 kg	45 mg BID x 4 days
	23-40 kg	60 mg BID x 5 days
	> 40 kg	75 mg BID x 5 days
Adults		75 mg BID x 5 days
* See dosing adjustment recommendations for those with impaired renal function		
Zanamivir (Relenza) – Inhaled Powder (2 inhalations = 10mg)		
Adults		10-mg BID x 5 days
Children (> 7 years)		10-mg BID x 5 days

CHILDREN UNDER 1 YEAR OF AGE

Oseltamivir was FDA approved in 2012 for use in children over two weeks of age. The AAP recommends that Oseltamivir may be used from the before two weeks of age because the likely benefits outweigh the potential harms.

PRETERM INFANT MEDICATION DOSING	
< 28 weeks postmenstrual age*	Consult pediatric infectious disease
28 - 38 weeks postmenstrual age	1.0 mg/kg/dose BID x 5 days
38 - 40 weeks postmenstrual age	1.5 mg/kg/dose BID x 5 days
> 40 weeks postmenstrual age.	3.0 mg/kg/dose BID x 5 days
*Postmenstrual age = gestational age + chronological age	

PROPHYLAXIS

Contacts who are at high risk of influenza complication should be advised to see their physician to obtain prophylactic antivirals. Chemoprophylaxis is given at the same dose in the table above but at a frequency of once a day for 10 days. It is not recommended for infants less than 3 months of age due to limited safety data.

ANTIVIRAL PROPHYLAXIS SHOULD BE CONSIDERED FOR:
Household or other close contacts of patients with confirmed, probable, or suspected influenza, who are high risk for complications
Health care workers with direct exposure to patient with confirmed or probable influenza during the person's infectious period

DISPOSITION

Outpatient management includes supportive care such as rest, hydration and analgesics (avoiding aspirin).

Patients and parents should be educated on how to limit spread by hand washing and covering up during sneezing and coughing. Patients should be advised to remain home for 24 hours after the fever resolves.

Patients whose symptoms resolve then reoccur should be advised to return as they are at risk for secondary bacterial infections.