Influenza Update: It Continues to Kill

William Sonnenberg, MD, FAAFP

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*This live CME session is supported by an educational grant from Seqirus USA Inc.*
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William Sonnenberg, MD, FAAFP

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Dr. Sonnenberg earned his medical degree from the University of Pittsburgh and completed his family medicine residency at McKeeseport Hospital in Pennsylvania. A past president of the Pennsylvania Academy of Family Physicians, he has been in private practice in the Titusville area since 1983. In 2017, he was a featured speaker about pneumonia and inflammatory bowel disease in three editions of the AAFP’s FP Audio™. His lectures at national meetings have been selected for publication by Audio-Digest seven times. 2019 marks his 12th time presenting at the AAFP’s annual meeting.
Learning Objectives

1. Evaluate patients for whom seasonal influenza vaccination is recommended and determine which form of the vaccine is most appropriate.

2. Counsel patients on the importance of seasonal influenza vaccination, emphasizing motivational interviewing for patients with concerns regarding vaccination safety and efficacy.

3. Administer appropriate diagnostic tests for influenza when necessary.

4. Select appropriate antiviral therapy and/or chemoprophylaxis for influenza and administer when indicated.

Audience Engagement System
Influenza in Philadelphia – Sept. 28, 1918

101 Years Ago this Month on Broad Street

- Flu arrived in Philadelphia on Navy freighter early September
- 200,000 showed for Liberty Parade, raising funds for WW1
- Physicians wrote letters against parade
- Vetoed by political leaders
Several Days Later

• Schools, theaters, churches, bars, pool rooms and dance halls permanently closed
• 12,000 died in next several weeks, 729 in a single day
• Only morgue, capacity for 36 bodies, held 500
• Nurses were kidnapped or bribed
• Coffins had to be guarded
• 500 Police failed to show for work

Consequences

• $1.00 fine for spitting on sidewalk
• Candy was sold as bogus influenza cures
• Bell Telephone only allowed emergency calls
• Commonwealth Brewing offered cold storage for bodies
• Prisoners, priests, seminary students dug graves
• 12,000 Pennsylvanians died
1918 Influenza Pandemic

1918-1919 Spanish Flu

• Type A virus (H1N1)
• >50 million deaths worldwide
• Killed 675,000 in USA
• Nearly half were young, healthy adults
• Believed started in rural Kansas in Spring, 1918
• Second wave was lethal wave, with almost all of worldwide deaths occurring in just 20 weeks

1918 Influenza Pandemic Devastation

- Killed more people worldwide than World War I
- Caused more deaths in USA than the Civil War, or all other US wars combined
- Cause ½ of deaths for American troops
- Most devastating epidemic in history
- Killed more people than the bubonic plague from 1347 to 1351
- Most deadly ages 20 to 40
- ↓ Average life span by 10 years in USA

Morens DM et al. J Infect Dis. 2007;195(7):1018

1918 Flu Was Different

- Bleed from mucous membranes
  - Nose, stomach, intestine, ears
- Edema and hemorrhage of lungs
- Strain produced 39,000 times more viral particles than standard H1N1

Tumpey TM et al. Science. 2005;310(5745):77
Age Mortality Different

Infectious Disease Mortality
1918 Flu De-Regulates Immune System

• Down-regulates RIG-1, causes immune system to “run wild”
• Releases unknown factor that promotes viral replication on massive scale
• More secondary bacterial infections
  • Strep, Staph

Taubenberger JK, Kash JC, Morens DM. Sci Transl Med
Influenza Mortality; Still a Killer

- Flu is 8th leading cause of death in the USA
- Flu kills as many or more Americans than breast cancer
- Killed 80,000 in USA during 2017-18 season, worse in 4 decades

CDC, November 2, 2018

Flu Burden in USA

- Deaths: 12,000-79,000
- Hospitalizations: 140,000-960,000
- Cases: 9,300,000-49,000,000

CDC, December 10, 2018
Peak Month of Flu Activity

1982-1983 through 2017-2018

Estimated U.S. Influenza Burden, By Season (2010 - 2018)

Source: https://www.cdc.gov/flu/about/burden
Influenza Virus

- RNA virus
- 99% mutation rate
- 8 genomes
  - One for neuraminidase, another for hemagglutinin
Type A Subtypes

- Two surface proteins
  - Hemagglutinin (H)
  - Neuraminidase (N)

Hemagglutinin

- Snugly binds to sialic acid on cell surface
- Pits form and virus enters cell in a vesicle
  - Hides from immune system
- Acid environment inside cell causes refolding of hemagglutinin and vesicle dissolves
  - Virus uncoats and fuses with cell
Neuraminidase

- 4 identical 6 blade propellers
- Break up sialic acid on cell surface
- Allows new viruses to leave dying cell

<table>
<thead>
<tr>
<th>Influenza Strains</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All ages groups</td>
<td>Humans only</td>
<td>Mild disease in children</td>
<td>Found in 2016</td>
</tr>
<tr>
<td></td>
<td>Humans and other animals</td>
<td>Primarily children</td>
<td></td>
<td>Cattle and pigs</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe disease</td>
<td>Lower antigenic variation</td>
<td></td>
<td>Humans?</td>
</tr>
<tr>
<td></td>
<td>High mutation rate</td>
<td>Myopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-3x less mutation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mutant Storm

• After 10 hours, 100,000 to 1,000,000 new influenza viruses erupt from cell.
• RNA viruses mutate 10,000 to 1,000,000 times faster than DNA viruses
• No “spellchecker”
• 99% of new viruses are mutations
• 1,000 to 10,000 can infect another cells

Transmissibility of Influenza

• 30% in households
• 33% in community
• 37% in school or workplace
• Range 6 feet via coughing, talking, or sneezing
• Shedding one day before and 7 days after symptoms begin

Audience Engagement Question #1

Which of the following is not a characteristic of influenza?

a. Dry cough
b. Myalgias of long muscles
c. Gradual onset
d. Headache

Clinical Features

- Incubation 2-3 days
- Infectious one day before symptoms
- Shedding for 5 days
- 7-15 days of illness
- 5-6 days of restricted activity
- 3 days of missed work

Symptoms

• Abrupt, memorable onset
• Fatigue
• Fever, chills, headache
• Myalgias of long muscles of back and extremities
• Dry cough
• Sore, dry throat
• Pain on ocular movement, tearing, burning

Physical Findings

• Appears hot and flushed
• Red throat, even with complain of severe sore throat
• Mild cervical adenopathy
• Generally unremarkable chest findings
Cold versus Influenza

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cold</th>
<th>Flu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Headache</td>
<td>Rare</td>
<td>Sudden/Severe</td>
</tr>
<tr>
<td>Fatigue</td>
<td>No, or mild</td>
<td>Yes, extreme</td>
</tr>
<tr>
<td>Stuffy nose</td>
<td>Common</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Common</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Cough</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Muscle Aches</td>
<td>Mild</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Respiratory Lining Damage

Normal Respiratory Lining  Three Days After Influenza
Lung Lining Leaks

Normal Lung Lining

Lung Lining After Influenza

Peak Months, 1976-2006

Source: MMWR 2007;56 (RR-6)
Why More Flu in Cold?
Low Humidity

- Low humidity's of 20-30% best for transmission
  - Particles dry and stay up
  - Travel longer distances
- Transmission blocked at 80% relative humidity
  - Particles settle too rapidly
  - Short distances (6 feet)

Lowen AC et al. PloS Pathog 3(10):e 151

Temperature Matters

- Transmission best at 5°C
- No transmission at 30°C
- Cold did not seem to effect innate immunity
- Cold thickened mucous and decreased cilia beats
- Guinea pigs shed 40 hours longer at 5°C than 20°C
Flu Survival on Surfaces

• 1-2 days on metal or plastic
• 5 minutes on skin
• 15 minutes on dry paper tissue
• Longer with mucous
  • 17 days on banknotes

Complications of Influenza
Audience Engagement Question #2

• Risk factors for complications include all except
  a. Long term acetaminophen treatment
  b. Immunosuppression
  c. Chronic heart disease
  d. Pregnancy

Risk Factors for Complications – the Usual Suspects

• Age ≥ 50 yrs.
• Nursing home/chronic care facilities
• Chronic pulmonary disease (e.g., asthma, COPD)
• Chronic cardiovascular disease
• Chronic metabolic diseases, renal dysfunction, hemoglobinopathy
• Immunosuppression
• Long-term aspirin therapy (ages 6 mos-18 yrs.)
• Second or third trimester pregnancy
Primary Influenza Pneumonia

- Predilection for elevated left atrial pressure and chronic lung disease
- Persistent, increasing symptoms
- High fever, dyspnea, maybe cyanosis
- CXR bilateral reticular haziness

Secondary Bacterial Pneumonia

- Risk over age 65
- Loss of cilia, damaged respiratory epithelium
- Exacerbation of fever and respiratory symptoms after initial improvement
- Pulmonary infiltrates, higher fevers, purulent sputum
Microbiology of Secondary Pneumonia

- *S. pneumoniae* 48%
  - Influenza increases risk 100x
- *H. influenza* 19%
- CA-MRSA in young, previously healthy
  - Mean age 16
  - Increased in epidemic years


Influenza and Acute Myocardial Infarction

- **6 times** higher during 7 days after lab confirmation of influenza
- Higher for older adults, influenza B
- Lesser elevations after other viral infections
- Reasons?
  - Systemic inflammation
  - Vasoconstriction
  - Increased metabolic demand

Myositis and Rhabdomyolysis

• Primarily in children
• 24 – 48 hours after resolution of symptoms
• Refusing to walk
• Ankles plantar-flexed, extreme tenderness of affected muscles
• Muscle enzymes 20-30 times normal
• Resolution 3-10 days
• Rhabdomyolysis rare


Diagnosis of Influenza
Audience Engagement Question #3

• The best diagnostic test for influenza is
  a. Rapid influenza test
  b. Immunofluorescence
  c. Reverse Transcription Polymerase Chain Reaction

Diagnosis of Influenza - Testing

<table>
<thead>
<tr>
<th>Rapid Influenza Diagnostic Tests (Fair)</th>
<th>Immunofluorescence (Good)</th>
<th>Reverse Transcription Polymerase Chain Reaction (RT-PCR) (Best)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-15 minutes</td>
<td>2-4 hours</td>
<td>45 minutes to several hours</td>
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<tr>
<td>50-70% sensitive, &lt;90% specific</td>
<td>Moderate sensitivity and high specificity</td>
<td>Very high sensitivity and specificity</td>
</tr>
<tr>
<td>Confirm negative results with RT-PCR</td>
<td>No typing A and B</td>
<td>Some differentiate A and B</td>
</tr>
<tr>
<td>No typing A and B</td>
<td></td>
<td>Other viruses</td>
</tr>
</tbody>
</table>
Cold v. Influenza - Simple

- Presence of cough and fever (≤ 37.8°) has positive predictive value of 79% when influenza is present in the populous


Testing Recommendations - IDSA

- Do not collect serological specimens for clinical management
- Do not use viral cultures for clinical management
- Rapid molecular assay testing preferred over rapid diagnostic testing
  - Can also test for multiple pathogens at same time
- Do not use rapid influenza testing in hospitalized patients

Timothy M Uyeki, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza, Clinical Infectious Diseases, Dec. 19, 2018
<table>
<thead>
<tr>
<th>High Risk – Really, Really Need Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pregnant</td>
</tr>
<tr>
<td>- Children younger than 5, more for those under 2</td>
</tr>
<tr>
<td>- Nursing home or chronic-care facility</td>
</tr>
<tr>
<td>- Chronic illnesses</td>
</tr>
<tr>
<td>- Immunodeficiencies</td>
</tr>
<tr>
<td>- HIV</td>
</tr>
<tr>
<td>- Chronic meds (i.e. steroids)</td>
</tr>
<tr>
<td>- Younger than 19 on long term aspirin therapy</td>
</tr>
<tr>
<td>- BMI &gt; 40</td>
</tr>
<tr>
<td>- Native Americans, including Alaskan Natives</td>
</tr>
<tr>
<td>- Healthcare workers or household contacts of those at high risk</td>
</tr>
<tr>
<td>- Household contacts and caregivers of infants younger than 6 months</td>
</tr>
</tbody>
</table>

CDC, August 27, 2018
Really Need Flu Vaccine

- 6 months and older

Vaccine Efficacy

- 70%-90% effective among healthy persons <65 years of age
- 30%-40% effective among frail elderly persons
- 50%-60% effective in preventing hospitalization
- 80% effective in preventing death
Seasonal Flu Vaccine Effectiveness

Flu Vaccine and MI

- 19% reduction in first MI
  - Sept – mid Nov – 21% reduction
  - Late vaccination - 12% reduction
- Pneumococcal vaccine – no help

Heart Failure and Influenza Vaccination

• 50% drop in death rate during flu season
• 20% drop rest of year

Flu Shot and Mortality

• First vaccination decreased death rate 10%
  • One death prevented for every 302 initial vaccinations
• Revaccination decreased death rate 24%
  • One death prevented for every 195 revaccinations
• Interrupting annual vaccination increases mortality 25%
Prevents Hospitalization

• Ages 2-4 years reduced risk of hospitalization 67%
• Ages 6 months to 23 months 48% reduction


Vaccine Formulations

**Standard Dose**
- Trivalent and Quadrivalent

**Over 65**
- High dose – 4 times antigen
- Adjuvanted

**Non-egg**
- Quadrivalent, cultured cells
- Recombinant DNA

**Live Viral**
- Quadrivalent, Cold adapted, ages 2-49
Vaccine Administration

- By end of October
- Can be given with minor respiratory illness
  - Avoid using LAIV with respiratory infections
- Can give inactivated vaccines with other vaccines
  - Don’t give LAIV with other live virus vaccines on the same day

Influenza Vaccine

- First developed in the 1940s
- Partially purified preps of influenza viruses grown in embryonated eggs
- Killed vaccines were highly pyrogenic and lacking in efficacy
- “Zonal ultracentrifuge” revolutionized purification process in 1960s – remains the basis of our current manufacturing process
Vaccine Side Effects

- Soreness at injection site (common, mild, and transient)
- Systemic and febrile reactions, especially in young children (infrequent)
- Immediate hypersensitivity reactions to egg protein (rare)
- Guillain-Barré syndrome (rare)

Who Should Not Receive TIV

- Allergic reaction to chicken eggs (welts, tongue swelling, difficulty breathing, loss of blood pressure, etc.)
- Previous serious reaction to influenza shot
- Rare paralytic disorder called Guillain-Barré Syndrome thought to be cause by a pervious influenza shot
- Current illness with fever
Who Should Not Receive Live Vaccine

• Younger than 5 years of age
• 50 years of age and older
• Chronic medical conditions – asthma, diabetes, immunosuppression, kidney failure
• Children and adolescents receiving long-term aspirin therapy
• Immunosuppression from any cause
• Pregnant women

Live Vaccine Contraindications and Precautions

• Severe (anaphylactic) allergy to egg or other vaccine components
• Hx of Guillain-Barré syndrome
• Moderate or severe acute illness
New ACIP Guidelines for Egg Allergy and Flu Vaccination

• Without history of anaphylaxis, no need for skin testing or divided doses
• No need to check ovalbumin
• Egg allergy patients should be observed for 30 minutes
• Providers should be equipped and trained to handle anaphylactic emergencies
More Severe in Pregnancy and Postpartum

- Increased heart rate and oxygen consumption
- Decreased lung capacity
- Diminished cell-mediated immunity

2009 H1N1 Pandemic and Pregnancy

- 1% of population, 5% of deaths
- 12% of pregnancy related deaths attributed to H1N1
- More hospitalizations, more ICU admissions

Siston AM et al. JAMA. 2010;303(15):1517.
Fetal Effects of Influenza

<table>
<thead>
<tr>
<th>Congenital Anomaly</th>
<th>Adjusted Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Anomaly</td>
<td>2.0</td>
</tr>
<tr>
<td>Cleft lip</td>
<td>3.2</td>
</tr>
<tr>
<td>Neural tube defect</td>
<td>3.3</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>5.7</td>
</tr>
<tr>
<td>Heart defect</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Vaccination in Pregnancy

- Risk of hospitalization more than 4 times higher than among nonpregnant women
- Risk of complications comparable to nonpregnant women with high-risk medical conditions
- ACIP recommends vaccination with inactivated influenza vaccine for ALL women who will be pregnant during influenza season
- Any trimester
- No live virus vaccination
Maternal Vaccination

• Randomized study of 340 mothers
  • Influenza
  • Pneumococcal vaccine (control)

• Infant benefit
  • 6 v. 16 cases of influenza, 63% effective
  • 29% reduction in URI with fever

• Maternal benefit
  • 36% reduction in URI with fever


Infant Influenza Hospitalizations

• 1510 hospitalized infants < 6 months

• Infants of vaccinated mothers during pregnancy were 45-48% less likely to be hospitalized

Hospitalization Risk and Vaccination

**Infants**
- 1510 hospitalized infants < 6 months
- Infants of vaccinated mothers during pregnancy were 45-48% less likely to be hospitalized

**Mothers**
- Pregnant women 18-50 from 2010 thru 2016
- 40% reduction in hospitalization

Clinical Infectious Diseases, Volume 68, Issue 9, 1 May 2019, Pages 1444–1453

Treating Influenza in Pregnancy

- Don’t delay treatment waiting for test results
- Antiviral prophylaxis within 48 hours of exposure
- Continue breastfeeding, express milk during separation
- Oseltamivir preferred for treatment
- Treat fever
  - Neural tube defects in first trimester
  - Fever during labor – neonatal seizures, CP, encephalopathy, neonatal death

Health Care Professionals

Benefits for Health Professionals

- Influenza Infection: -88%
- Sick Day due to Respiratory Infection: -28%
- Lost Days from work: -41%
- Patient Mortality: -41%

Talbot TR et al. Inf Control Hosp Epidemiol 2005 26:862-890
Neonatal ICU Event

• 19 babies in Ontario NICU, one died in 2000
• Only 15% of the workers vaccinated

AAFP Policy – June 2011

• All health care personnel to receive the vaccine each year
• Exceptions based only on medical or religious reasons, not on personal preference
Vaccination in the Elderly

Vaccination in Elderly

- Randomized, placebo controlled
- 2000 patients older than 60
- NNT 23
- Relative risk 0.43
Influenza in the Elderly (65 and older)

- 70% - 85% of deaths
- 54%-70% of hospitalizations
- Weaker immune response to vaccination
- Possible diminishing effect of annual vaccination

CDC, October 19, 2018

High Dose Flu Vaccine

- Indicated for 65 and older
- 4 times antigen
- 24.2% more effective in preventing flu
- 11% lower risk of hospitalization
- More pain, redness, myalgias, malaise

Lancet Respiratory. 5:9, P738-746, SEPTEMBER 01, 2017
Adjuvanted Influenza Vaccine

- Also indicated for 65 and older
- Standard dose flu vaccine with adjuvant
- More pain, redness, headache, myalgias, malaise
- 6% lower hospitalizations
- No comparison studies

IDWeek 2018, October 2018
New York Nursing Home

- 65 residents sickened in 1991-92
- 19 Hospitalized
- Two died
- Only 10% of the workers vaccinated

Vaccine In Nursing Home

*Inactivated influenza vaccine. Genesee County, MI, 1982-1983*
Influenza in the Nursing Home

- Vaccinate
- Test
- Infection control
- Antiviral treatment
- Antiviral chemoprophylaxis

Nursing Home Vaccination

- Vaccinate workers, presently 67.4%
  - Less transmission
  - Less absenteeism, less staff illness
  - Lower death rate in residents
- Vaccinate residents
  - Need informed consent, not necessarily signed

CDC, October 30, 2018
Nursing Home Standard and Droplet Protection

- Standard Precautions
  - Gloves, gown, hand hygiene
- Droplet precautions
  - Ill residents in private room
  - Facemask on resident during transport
  - Communicate

Treat Confirmed or Suspected Infection

- Treatment should not wait for lab tests
- Use oseltamivir, zanamivir, peramivir (IV)
- Do not use amantadine or rimantadine
  - High resistance for influenza A
- Do not administer steroids for influenza, unless for other reasons
- Works best in first 2 days of illness

Timothy M Uyeki, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza, Clinical Infectious Diseases, Dec 19, 2018
Antiviral Chemoprophylaxis for Outbreak

• 2 ill patients within 72 hours, one laboratory-confirmed
• Treat all non-ill residents
• Treat for 2 weeks minimum and for one week after identification of last known case
• Consider prophylaxis for unvaccinated personnel

Timothy M Uyeki, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza, Clinical Infectious Diseases, Dec 19, 2018

Treatment of Influenza
Contact Treatment

• Stay home
  • For 7 days after onset or 24 hours after resolution of symptoms
  • Contact Provider before seeking care in office or hospital
  • Mask
• Avoid contact with sick
• Wash hands often
• Avoid touching mucous membranes

Provider Preventive Measures

• Hand washing
• Face masks
• If implemented within 36 hours, reduces household transmission by 67%

Ann Intern Med. 2009;151(7):437
Preparation of Oscillococcinum

Decapitate duck
Remove 35 grams of heart and 15 grams of liver
Mix with pancreatic juice and glucose
Allow to ferment for 40 days
Dilute, dilute, dilute...

Table of Dilution

<table>
<thead>
<tr>
<th>Dilution</th>
<th>Ratio</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1C</td>
<td>1:100</td>
<td></td>
</tr>
<tr>
<td>3C</td>
<td>$10^{-6}$</td>
<td></td>
</tr>
<tr>
<td>12C</td>
<td>$10^{-24}$</td>
<td>Unlikely single molecule remains</td>
</tr>
<tr>
<td>30C</td>
<td>$10^{-60}$</td>
<td>Standard homeopathic dilution, to get single molecule, 2 billion doses per second to 6 billion people for 4 billion years</td>
</tr>
<tr>
<td>200C</td>
<td>$10^{-400}$</td>
<td>Dilution of Oscillococcinum</td>
</tr>
</tbody>
</table>
Maybe It Works? Not!

- Wild duck heart and liver
- Main outcomes: Influenza symptoms (temperature, cough, chills, pain, sore throat, rhinitis), duration, global assessment of improvement, medication use.
- 4 treatment trials (2 of high quality), no significant difference
- 3 prevention trials, no difference

http://www.medicine.ox.ac.uk/bandolier/booth/alternat/AT017.html

Antiviral Treatment

- Decide, don’t wait for laboratory confirmation
- Vaccinated patient still can get flu
- Treat within 48 hours of onset
  - 13% of patients contact doctor within 48 hours
- After 48 hours, still treat those with high risk of complications

CDC, November 28, 2018
High Risk for Influenza Complications

- Unvaccinated infants 12-24 months
- Asthma, COPD, CF
- Significant cardiac disease (not HTN)
- Immune suppressed
- Sickle cell, other hemoglobinopathies
- Native Americans and Alaskan Natives
- Chronic renal disease
- Chronic liver disease
- Active cancer
- Diabetes
- Neuromuscular disease
- Over age 65
- Extreme obesity, BMI≥40
- Nursing homes


Indications for Treatment

- All hospitalized patients with influenza, regardless of duration
- Outpatients with severe or progressive illness, regardless of duration
- High risk patients

Advisory Committee on Immunization Practices' and IDSA's guidelines
Consider for Treatment

• Outpatients with illness within 48 hours of presentation
• Symptomatic household contacts of high risk patients
• Symptomatic health care workers for high risk patients

Benefits of Treatment

• Shortens duration of symptoms ½ to 3 days
• May reduce severity and incidence of complications
Three Antiviral Classes – Six Meds

• **M2 inhibitors** - only active against Influenza A
  • Amantadine
  • Rimantadine
• **Neuraminidase inhibitors** - active against Influenza A and B
  • Zanamivir *only approved for the treatment, not prevention of the flu
  • Oseltamivir
  • Peramivir – IV single dose
• **Endonuclease inhibitor** – Baloxavir marboxil, active against A and B

M2 Inhibitors

• Amantadine and rimantadine
• Target M2 ion channel, block entry into cell
• Only for influenza A
• >99% resistance to recent strains
• Currently **not recommended** for prophylaxis or treatment of current strains
• CNS side effects in elderly
Antiviral Prophylaxis

- Certain individuals with known contact during their infectious period
  - High risk patients
  - Healthcare workers, public health workers, first responders
- 70-90% effective

Neuraminidase Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Preamivir</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>Inhaled</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Use</td>
<td>Oral</td>
<td>Inhaled</td>
<td></td>
</tr>
<tr>
<td>first 48</td>
<td>Use in first 48 hours</td>
<td>1000 times MIC in lungs</td>
<td>Single dose</td>
</tr>
<tr>
<td>hours</td>
<td>Preferred in pregnancy</td>
<td>Bronchospasm risk</td>
<td>Diarrhea (8%)</td>
</tr>
<tr>
<td>Preferred</td>
<td>Preferred in pregnancy</td>
<td>Age ≥ 7 years</td>
<td>Skin reactions</td>
</tr>
<tr>
<td>in pregnancy</td>
<td></td>
<td>Age ≥ 7 years</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 14</td>
<td>Age &gt; 14 days</td>
<td></td>
<td>$1,000 per dose</td>
</tr>
<tr>
<td>days</td>
<td>Generic available</td>
<td></td>
<td>Age ≥ 2 years</td>
</tr>
<tr>
<td>Generic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>available</td>
<td></td>
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</tr>
</tbody>
</table>
Oseltamivir Efficacy

- Shortens duration 17 hours in adults
- 29 hours in children
- Otitis media 12% v. 21%
- Antibiotics use 31% v. 41%
- May shorten duration if given within 12 hours


Zanamivir

- Oral inhalation
- Contraindicated in asthma and other chronic lung disease
- Shortens duration 1-3 days
  - 1.3 days in lab-confined influenza in heathy pts. ≤ 65 years
  - 2 days ≥ 65 years with comorbidities

BMJ. 2003;326(7401):1235.
Neuraminidase Inhibitors in Pregnancy

- 350 severely ill pregnant women during H1N1 epidemic
  - Half had HTN, Diabetes or asthma
- 86% of those who died took antivirals v. 95% of survivors
- 7% of those who died had antiviral within 2 days v. 41% of survivors

MMWR 60(35); 1193-1196

Baloxavir

- Inhibitor of influenza cap-dependent endonuclease
- Impacts replication
- Single dose, ≥ 12 years, within 48 hours
- Symptom relief similar to oseltamivir
- Greater viral load reduction than oseltamivir
- May work in combination with neuraminidase inhibitors
- AWP $90 per dose

Statins

• Surveillance study of 3043 hospitalized patients
• 41% lower risk of death


Oseltamivir, Naproxen, Clarithromycin

• Open-label, hospitalized patients with severe H3N2 influenza
  • Two days of oseltamivir, naproxen, and clarithromycin followed by 3 days of oseltamivir alone
  • 5 days of oseltamivir
• Combination v. oseltamivir
  • 30 day mortality (0.9% v. 8.2%)
  • 90 day mortality (1.9% v. 10%)
  • Shorter hospital stay
  • Less ICU admission

Glucocorticoids?

- Meta-analysis shows increased mortality (OR 3.06, 95% CI 1.58-5.92)
- Do not use unless clear, separate indication

Uyeki TM et al. Clin Infect Dis. 2018

Practice Recommendations

- Review the 6 various influenza preparations and stock 2-3.
- Be aggressive in vaccinating all pregnant mother with inactivated flu vaccine during flu season
- Consider egg-free preparations for the egg allergic patient, but may give egg-derived vaccine with observation
- Be aggressive in advocating vaccination of all health care worker for their own benefit and the benefit of the patients they care for.
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Questions