SEASONAL INFLUENZA
When, Who, and How to Manage

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LEARNING OBJECTIVES

1. Diagnose and promptly treat influenza in accordance with national guidelines and emerging evidence

2. Use approved antiviral medications to better treat influenza based on efficacy and safety data in order to reduce symptoms, prevent associated complications, and reduce the burden of disease

DISCLOSURES

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The following relationships exist related to this presentation:
Robert H. Hopkins Jr, MD:
Charles Vega, MD: Consultant for Genentech.

Off-Label/Investigational Discussion
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2. Use approved antiviral medications to better treat influenza based on efficacy and safety data in order to reduce symptoms, prevent associated complications, and reduce the burden of disease

DIAGNOSIS OF INFLUENZA
COMMON SIGNS/SYMPTOMS

Atypical Presentations
Infants (e.g., sepsis-like syndrome)
Elderly (e.g., confusion)

Nonproductive cough
Headache
Myalgias
Fever

CDC.gov (2019). Seasonal Influenza Vaccine Effectiveness, 2018-2019 | CDC.

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PERSONS AT HIGHER RISK FOR INFLUENZA COMPLICATIONS

- Children < 5 years old
- Individuals < 19 years on long-term aspirin therapy
- Adults ≥ 65 years old
- Morbidly obese persons (BMI ≥ 40 kg/m²)
- Pregnant women or ≤ 2 weeks postpartum
- American Indian/Alaska Native heritage
- Residents of nursing homes/chronic care facilities
- Immunosuppressed patients
- Patients with chronic medical conditions, including pulmonary, cardiovascular, renal, hepatic, hematological, metabolic, neurologic, or neurodevelopmental disorders

BACTERIAL CO-INFECTION

CLINICAL CONSIDERATIONS

- Adults typically have symptoms for about 3 days
  - Most show signs of improvement by this point
- Complete recovery may take 10–14 days
  - Longer in older adults

POSSIBLE CO-INFECTION

- Fevers for more than 3–5 days
- Worsening symptoms or rapid clinical deterioration
- Most common pathogens:
  - *Streptococcus Pneumoniae*
  - Staphylococcus (MRSA/MSSA)
  - Group A Streptococcus
- Consider ID consult

COMPLICATIONS OF INFLUENZA

- **NEUROLOGIC**
  - Encephalitis
  - Seizures
  - Stroke

- **PULMONARY**
  - Worsening of COPD & Asthma
  - Pneumonia
  - Bronchiolitis
  - Croup
  - Respiratory failure
  - Invasive bacterial co-infection

- **CARDIAC**
  - Congestive heart failure
  - Acute myocardial infarction
  - Myocarditis
  - Pericarditis

- **MUSCULOSKELETAL**
  - Myositis
  - Rhabdomyolysis

- **MULTI-ORGAN FAILURE**
  - Septic shock
  - Renal failure
  - Respiratory failure

WHEN SHOULD I TEST FOR INFLUENZA?

(1) Shieh WJ, et al., J. Am J Pathol. 2010;177:166-75

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GUIDE FOR CONSIDERING INFLUENZA TESTING

WHEN VIRUSES ARE CIRCULATING IN THE COMMUNITY (REGARDLESS OF INFLUENZA VACCINATION HISTORY)

Does the patient have signs/symptoms suggestive of influenza, including atypical clinical presentation or findings suggestive of complications associated with influenza?

Yes

Is the patient being admitted to the hospital?

No

Will influenza testing results influence clinical management?

No

Influenza testing probably NOT indicated

Consider other etiologies

Yes

Test for influenza

Start empiric antiviral treatment for hospitalized patients while results are pending

Influenza clinically diagnosed

Start empiric antiviral treatment if the patient is in a high-risk group for influenza complications or has progressive disease

Advise close follow-up if worsening

https://www.cdc.gov/flu/professionals/diagnosis/consider-influenza-testing.htm

INFLUENZA DIAGNOSTIC TESTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Time to Results</th>
<th>Performance</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid diagnostic test</td>
<td>Antigen detection</td>
<td>&lt; 15 min</td>
<td>Low to moderate sensitivity; High specificity</td>
<td>ALL TESTS: Negative results may not rule out influenza; most assays are approved for point-of-care use</td>
</tr>
<tr>
<td>Rapid molecular assay</td>
<td>Viral RNA detection</td>
<td>15-30 min</td>
<td>Moderate to high sensitivity; High specificity</td>
<td>Immunofluorescence assay requires trained laboratory personnel with fluorescent microscope in a clinical laboratory</td>
</tr>
<tr>
<td>Immunofluorescence assay</td>
<td>Antigen detection</td>
<td>1-4 hours</td>
<td>Moderate sensitivity; High specificity</td>
<td></td>
</tr>
<tr>
<td>Molecular assay</td>
<td>Viral RNA detection</td>
<td>60-80 min for some assays; up to 4-8 h for others</td>
<td>High sensitivity; High specificity</td>
<td></td>
</tr>
<tr>
<td>Tissue cell viral culture</td>
<td>Virus isolation</td>
<td>3-10 days</td>
<td>High sensitivity; High specificity</td>
<td></td>
</tr>
</tbody>
</table>

Molecular assays are the most accurate influenza tests

https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm

INFLUENZA TESTING

...when influenza viruses are circulating in the community...

INFLUENZA TESTING IS NOT NEEDED

to confirm the clinical diagnosis

or to decide whether to prescribe antiviral medications

TESTING RECOMMENDED IF WILL CHANGE TREATMENT OR PATIENT REQUIRES HOSPITALIZATION

Molecular assay = Best

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

WHEN SHOULD I START ANTIVIRALS TO TREAT INFLUENZA?

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31-year-old Female Walks into your clinic with a 60hr history of influenza-like illness.

- Diagnosed with breast cancer 6 months ago
- Currently on neoadjuvant chemotherapy
- You strongly suspect influenza

**RATIONALE**

- **NO:** Antivirals should be initiated only if influenza testing is positive
- **NO:** Treatment should only be started within 24 hours of illness onset
- **NO:** Treatment is only effective if started within 48 hours of illness onset
- **YES:** Benefits of antivirals are the same in all populations, no matter when treatment is started after illness onset

- **NO:** Flu testing is not needed to initiate treatment
- **NO:** Antivirals can be prescribed at anytime during the course of illness based on clinical judgment but are most effective if started within 48 hours

**Mortality is reduced when treatment is initiated early**

<table>
<thead>
<tr>
<th>Treatment Initiation after illness onset</th>
<th>Survival Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 days ≤ 48 hrs</td>
<td>~95%</td>
</tr>
<tr>
<td>≥ 5 days ≤ 120 hrs</td>
<td>~85%</td>
</tr>
</tbody>
</table>

**When to start antivirals in outpatients**

- **≤ 48 hours after illness onset**
  - Uncomplicated influenza
    - Use clinical judgment
  - Suspected/confirmed influenza in a group at high risk for complications
  - Progressive disease who do not require hospitalization

- **> 48 hours after illness onset**

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CLINICIANS INFREQUENTLY PRESCRIBE ANTIVIRAL TREATMENT IN THE OUTPATIENT SETTINGS (2011-2016 INFLUENZA SEASONS)

<table>
<thead>
<tr>
<th>Year</th>
<th>All High-Risk Patients Prescribed Neuraminidase Inhibitor (NAI)</th>
<th>High-Risk Patients Presenting Early</th>
<th>High-Risk Patients Presenting Early With Laboratory Confirmed Influenza</th>
<th>Patients Prescribed Antibacterials with Laboratory Confirmed Influenza (on research testing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-2012</td>
<td>2.0%</td>
<td>9%</td>
<td>36%</td>
<td>37% of high-risk patients with rRT-PCR-confirmed influenza received a prescription for an antiviral medication</td>
</tr>
<tr>
<td>2012-2013</td>
<td>3.0%</td>
<td>9%</td>
<td>19%</td>
<td>29% of patients in outpatient setting with influenza were prescribed antibacterials</td>
</tr>
<tr>
<td>2013-2014</td>
<td>4.3%</td>
<td>7%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>2014-2015</td>
<td>8%</td>
<td>8%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>2015-2016</td>
<td>5%</td>
<td>12%</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

WHICH ANTIVIRALS SHOULD I USE TO TREAT INFLUENZA?

ANTIVIRALS FOR INFLUENZA

- ✓ Neuraminidase inhibitors (NAIs)
- ✓ Cap-dependent endonuclease inhibitor
- ✗ Adamantanes (Not recommended)

NEURAMINIDASE INHIBITORS

MECHANISM OF ACTION

1. Viral invasion
2. Membrane fusion
3. Initiation of mRNA synthesis (cap-dependent endonuclease)
4. Virion formation
5. Virion release

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**Neuraminidase Inhibitors**

**Uncomplicated Influenza**

<table>
<thead>
<tr>
<th></th>
<th>Oseltamivir (Tamiflu)</th>
<th>Zanamivir (Relenza)</th>
<th>Peramivir (Rapivab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult dosage</td>
<td>75 mg PO BID x 5 days</td>
<td>2 inhalations BID x 5 days</td>
<td>600 mg IV once</td>
</tr>
<tr>
<td>Pediatric dosage</td>
<td>30-75 mg PO BID x 5 days</td>
<td>≥ 7 yrs: 2 inhalations BID x 5 days</td>
<td>2-12 yrs: 12 mg/kg (max 600 mg) IV once</td>
</tr>
<tr>
<td></td>
<td>≥ 13 yrs: 600 mg IV once</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosage of renal impairment</td>
<td>Adults: CrCl 30-60 mL/min: 30 mg BID</td>
<td>No dosage adjustment required</td>
<td>2-12 yrs</td>
</tr>
<tr>
<td></td>
<td>CrCl &gt; 30 mL/min: 30 mg QD</td>
<td>CCl 30-49 mL/min: 4 mg/kg once</td>
<td>CCl 10-29 mL/min: 2 mg/kg once</td>
</tr>
<tr>
<td></td>
<td>≥ 13 yrs:</td>
<td>CCl 30-49 mL/min: 200 mg once</td>
<td>CCl 10-29 mL/min: 100 mg once</td>
</tr>
<tr>
<td>Cost</td>
<td>Generic: $98.60</td>
<td>$59.00</td>
<td>$950.00</td>
</tr>
<tr>
<td></td>
<td>Tamiflu: $151.90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Neuraminidase Inhibitors**

**Efficacy**

- Decrease the time to first alleviation of symptoms of influenza-like illness by...

- **Oseltamivir (Tamiflu)**
  - Adults: 16.8 - 17.8 hours
  - Children: 29 hours

- **Zanamivir (Relenza)**
  - Adults: 14.4 hours
  - Children: Not significant

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**Neuraminidase Inhibitors**

**Safety Considerations**

- **Oseltamivir (Tamiflu) → Nausea and vomiting**
  - Does not generally result in discontinuation of therapy
  - Taking the drug with food may minimize GI adverse effects

- **Zanamivir (Relenza) → Bronchospasm and a decline in respiratory function** in patients with chronic respiratory disorders (i.e. asthma, COPD)
  - Should NOT be used in patients with underlying airway disease (manufacturer warning)

- **Neuropsychiatric events** are rare and not proven to be associated with NAIs

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Presents with ~ 24 hours of influenza-like illness

- 20-weeks pregnant
- History of asthma (daily inhaler use)
- You decide to treat her with an antiviral

**RATIONALE**

- **Zanamivir** (Relenza)
  - Not 1st choice agent in pregnancy
  - Contraindicated in this patient with underlying respiratory disease given risk of bronchospasm
- **Peramivir** (Rapivab)
  - Not recommended in pregnant patients by CDC
- **Oseltamivir** (Tamiflu)
  - Oseltamivir is recommended over inhaled zanamivir
  - Not associated with any adverse pregnancy or birth outcomes
- **Amantadine** (Symmetrel)
  - No longer recommended for treatment of influenza due to high resistance rates
- **Baloxavir marboxil** (Xofluza)
  - No data on use in pregnancy but no adverse maternal or embryo-fetal effects in animal studies
- Any of the above could be used

**ANTIVIRALS PREGNANCY**

Antivirals for influenza in pregnancy

(NOT a contraindication)

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

**CAP-DEPENDENT ENDONUCLEASE INHIBITORS MECHANISM OF ACTION**

1. Viral invasion
2. Membrane fusion
3a. Initiation of mRNA synthesis (cap-dependent endonuclease)
3b. Genomic RNA replication
4. Virion formation
5. Virion Release

Neuraminidase inhibitor

Cap-dependent endonuclease inhibitor (baloxavir marboxil)

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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**BALOXAVIR MARBOXIL (XOFLUZA)**

- **Treatment** of influenza A and B & avian-origin H5N1 and H7N9 influenza viruses
  (Not approved for chemoprophylaxis)
- Single oral dose
- Adults and children > 12 years old
- Symptomatic for ≤ 48 hours
  More effective if given as soon possible (≤ 24 hrs of symptom onset)


**BALOXAVIR MARBOXIL (XOFLUZA)** ASSOCIATED WITH A MORE RAPID DECLINE IN VIRAL LOAD THAN PLACEBO AND OSELTAMIVIR (TAMIFLU)

Faster decline in viral load
Faster time to cessation of viral shedding

**BALOXAVIR MARBOXIL (XOFLUZA) DECREASED DURATION OF FLU SYMPTOMS AND DURATION OF FEVER

Duration of flu symptoms
↓ by > 1 day*  
Duration of fever
↓ by nearly 1 day*

*Similar to oseltamivir (Tamiflu)

**BALOXAVIR MARBOXIL (XOFLUZA)*
HIGH RISK POPULATIONS

<table>
<thead>
<tr>
<th></th>
<th>Time to improvement of influenza symptoms (hours)</th>
<th>Median time to cessation of viral shedding (hours)</th>
<th>Systemic antibiotic use (%)</th>
<th>Influenza-related complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BXM</td>
<td>73</td>
<td>46</td>
<td>7.5</td>
<td>2.8%</td>
</tr>
<tr>
<td>Placebo</td>
<td>102</td>
<td>96</td>
<td>10.4%</td>
<td></td>
</tr>
</tbody>
</table>

The incidence of any or serious adverse events did not differ significantly across the groups

BXM: Baloxavir marboxil

*I: Under FDA review for additional indication for treatment of influenza in individuals at high risk for influenza-related complications in individuals ≥ 12 yrs

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BALOXAVIR MARBOXIL (XOFLUZA)

SAFETY

Compared to oseltamivir...

Baloxavir marboxil is equally safe and potentially associated with fewer AEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Baloxavir marboxil (%)</th>
<th>Placebo (%)</th>
<th>Oseltamivir (Tamiflu) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>4.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2.6</td>
<td>5.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1.5</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.3</td>
<td>1.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.1</td>
<td>2.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>1.0</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>ANY ADVERSE EVENT</td>
<td>20.7</td>
<td>24.6</td>
<td>24.8</td>
</tr>
</tbody>
</table>


ANTIVIRAL RESISTANCE

- Currently low resistance to...
  - Oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab), and baloxavir marboxil (Xofluza)
- Resistance can emerge at any time, as well as during or after treatment in some patients (e.g., immunocompromised)

Weekly surveillance data on antiviral resistance

CAN I USE ANTIVIRAL AGENTS TO PREVENT INFLUENZA?

Calls your office to inform you that her boyfriend came down with influenza today, the day after they spent an entire day together (2 days ago)

- She refused the flu vaccine
- History of COPD
- Asks whether she should be tested or treated for influenza

73-year-old Female

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**AUDIENCE RESPONSE QUESTION**

Which of the following would you recommend to/her now?

1. Order a molecular assay to test for influenza
2. Prescribe oseltamivir (Tamiflu) to prevent influenza
3. Prescribe zanamivir (Relenza) to prevent influenza
4. Prescribe baloxavir marboxil (Xofluza) to prevent influenza
5. No treatment is necessary unless she develops symptoms

**CHEMOPROPHYLAXIS WITH NAIS**

NAIs are ~70% to 90% effective in preventing influenza, however…

- [CDC](https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm)

<table>
<thead>
<tr>
<th>CHEMOPROPHYLAXIS WITH NAIS CANDIDATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at high risk of influenza complications</td>
</tr>
<tr>
<td>- ≤ 2 weeks following vaccination after exposure to a person with influenza</td>
</tr>
<tr>
<td>- Cannot receive influenza vaccine due to a contraindication after exposure to a person with influenza</td>
</tr>
<tr>
<td>- Persons with severe immune deficiencies</td>
</tr>
<tr>
<td>- Persons who might not respond to influenza vaccination</td>
</tr>
<tr>
<td>- i.e. those receiving immunosuppressive medications, after exposure to a person with influenza</td>
</tr>
<tr>
<td>- Control outbreaks among high risk persons in institutional settings</td>
</tr>
</tbody>
</table>

**PROPHYLACTIC TREATMENT OF INFLUENZA**

<table>
<thead>
<tr>
<th>Oselementiv (Tamiflu)</th>
<th>Zanamivir (Relenza)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg PO once/day x 7 days</td>
<td>2 inhalations once/day x 7 days</td>
</tr>
</tbody>
</table>

- **Pediatric dosage**
  - 30-75 mg PO once/day x 7 days

- **Dosage for renal impairment**
  - Adults: CrCl 30-60 mL/min: 30 mg QD
  - CrCl > 10-30 mL/min: 30 mg every other day

- **Baloxavir Marboxil (Xofluza) & peramivir (Rapivab)**
  - NOT FDA-approved for prophylaxis

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CHEMOPROPHYLAXIS WITH NAIs

TIMING OF TREATMENT

Prophylaxis generally **NOT recommended if >48 hours** have elapsed since the first exposure to a person with influenza

*Close monitoring and early antiviral treatment if symptoms develop*

Medication taken **each day** for the duration of potential exposure to a person with influenza

*Continued for 7 days after the last known exposure*


LET’S REVIEW…

**Testing**

**Candidates**

**Approved antivirals**

**Timing of treatment**

**Chemoprophylaxis**

**Safety**

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Approved antivirals for treatment of influenza

- **NAIs**
- **Cap-dependent endonuclease inhibitor (baloxavir marboxil)**
- **Adamantanes**
  - Adamantanes are **NOT recommended** for treatment of influenza A virus infection

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Let’s Review…

Testing
Candidates
Approved antivirals
Timing of treatment
Chemoprophylaxis
Safety

Start antivirals as soon as possible
- Ideally within 48 hours after illness onset
- Most effective if started within the first 24 hours of symptoms and less effective if begun 24-48 hours after symptoms appear

Let’s Review…

Testing
Candidates
Approved antivirals
Timing of treatment
Chemoprophylaxis
Safety

Not routinely recommended except in individuals in whom vaccination is contraindicated or who are not expected to benefit

Let’s Review…

Testing
Candidates
Approved antivirals
Timing of treatment
Chemoprophylaxis
Safety

Pregnancy is NOT a contraindication to using NAs or baloxavir marboxil

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