New in the treatment of influenza

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Influenza epidemic

❖ The annual influenza epidemic substantially affects health care systems worldwide.

❖ The extent of the morbidity and mortality in any given year reflects the **efficacy and coverage of vaccination and efficacy of treatment.**
Treatments of influenza

- Treatments for influenza may either
  1) directly target the influenza virus itself;
  2) or instead they may just offer relief to symptoms of the disease, while the body's own immune system works to recover from infection.
Symptomatic treatment

- Get plenty of **rest**
- Drink a lot of **liquids**
- Do not **smoke or drink alcohol**
- Consider over-the-counter medications to **relieve flu symptoms**
- **Remain alert for emergency warning signs**
  - Difficulty breathing or shortness of breath
  - Pain or pressure in the chest or abdomen
  - Dizziness
  - Confusion
  - Severe or persistent vomiting
Nutritional supplements

- **Malnutrition** can reduce the ability of the body to resist infections and is a common cause of immunodeficiency in the developing world.

- For instance, in a study in Ecuador, micronutrient deficiencies were found to be common in the elderly, especially for vitamin C, vitamin D, vitamin B-6, vitamin B-12, folic acid, and zinc, and these are thought to weaken the immune system or cause anemia and thus place people at greater risk of respiratory infections such as influenza.
Antiviral drugs

- The main classes of Antiviral drugs used against influenza:
  1) Neuraminidase inhibitors, such as zanamivir and oseltamivir
  2) Polymerase acidic endonuclease inhibitors such as baloxavir
  3) Inhibitors of the viral M2 protein such as amantadine and rimantadine.

- These drugs can reduce the severity of symptoms if taken soon after infection and can also be taken to decrease the risk of infection.
- However, virus strains have emerged that show drug resistance to some classes of drug.
Recommended Antivirals 2020-2021

Four FDA-approved antivirals are recommended for use in the United States

- Neuraminidase inhibitors:
  - oseltamivir (oral)
  - zanamivir (inhaled)
  - peramivir (intravenous)

- Cap-dependent endonuclease inhibitor: baloxavir marboxil (oral)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Oral</td>
<td>Any age</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Inhaled</td>
<td>≥ 7 years</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Intravenous</td>
<td>≥ 2 years</td>
</tr>
<tr>
<td>Baloxavir</td>
<td>Oral</td>
<td>≥ 12 years</td>
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</table>
Amantadine & Rimantadine

- Amantadine and rimantadine were used for the treatment and prevention of influenza A.
- The antiviral mechanism of action is antagonism of the influenza virus A M2 protein channel.
- Their use is no longer recommended due to widespread drug resistance.
Oseltamivir

- under the brand name Tamiflu
- It was the first neuraminidase inhibitor available by mouth
- It is recommended for people who have complications or are at high risk for complications
Persons who are at high risk of complications from influenza

<table>
<thead>
<tr>
<th>Persons at High Risk of Complications</th>
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<tbody>
<tr>
<td>Children aged &lt;5 years, and especially aged &lt;2 years</td>
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<tr>
<td>Adults aged ≥65 years</td>
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<tr>
<td>Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)</td>
</tr>
<tr>
<td>Persons with immunosuppression, including that caused by medications or by HIV infection&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women who are pregnant or postpartum (within 2 weeks after delivery)</td>
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<tr>
<td>Children and adolescents through 18 years who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection</td>
</tr>
<tr>
<td>American Indian/Alaska Native people&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Persons with extreme obesity (ie, body mass index ≥40 kg/m²)</td>
</tr>
<tr>
<td>Residents of nursing homes and other chronic care facilities</td>
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</table>
Zanamivir

- To treat and prevent influenza A and B.
- under the trade name Relenza as a powder for oral inhalation.
- It not recommended for treatment or prophylaxis of seasonal influenza in individuals with asthma or COPD due to inducing bronchospasms.
Peramivir

• (trade name Rapivab)
• It is approved for intravenous administration
Baloxavir marboxil

- Under the brand name **Xofluza**
- for treatment of **influenza A** and **influenza B** flu (not for prevention)
- It is taken as a single dose by mouth
- **Contraindications:** Baloxavir should not be co-administered with dairy products, or laxatives, antacids, or oral supplements containing calcium, iron, magnesium, selenium, aluminum or zinc.
Baloxavir marboxil

- Oral baloxavir marboxil was approved in October 2018 by the U.S FDA for treatment of acute **uncomplicated influenza within 2 days** of illness onset in people 12 years and older who are otherwise healthy, or at high risk of developing influenza-related complications.
Baloxavir marboxil

- There are no available efficacy or safety data for baloxavir in pregnant women, and there are no available data on the presence of baloxavir in human milk.

✓ So, **CDC does not recommend use of baloxavir for treatment of influenza in pregnant women or breastfeeding mothers.**

❑ Only one randomized clinical trial has compared baloxavir to oseltamivir for treatment of influenza B. This study found that baloxavir treatment was superior to oseltamivir among outpatients with influenza B virus infection.
Baloxavir marboxil

- There are no available efficacy, safety, or resistance data for baloxavir monotherapy of influenza in severely immunosuppressed patients and emergence of resistance during treatment is a concern because of prolonged influenza viral replication in these patients.

✓ So, **CDC does not recommend use of baloxavir for monotherapy of influenza in severely immunosuppressed persons.**

- There are no available data on the use of baloxavir for treatment of influenza more than 2 days after illness onset.
Umifenovir

- the brand name **Arbidol**
- For the treatment of flu used in Russia and China
- **It is not approved by the US FDA** for the treatment or prevention of influenza
- available as tablets, capsules and syrup.
- This prevents viral entry to the target cell, and therefore protects it from infection.
Empirical antiviral treatment

- Empirical antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who:
  - is hospitalized
  - has severe, complicated, or progressive illness; or
  - is at higher risk for influenza complications.

- Decisions about starting antiviral treatment for these patients should not wait for laboratory confirmation of influenza virus
# Antiviral agents for treatment and prophylaxis of influenza

<table>
<thead>
<tr>
<th>Antiviral agents</th>
<th>Treatment doses</th>
<th>Prophylaxis doses</th>
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<tbody>
<tr>
<td>Oseltamivir</td>
<td>75 mg / BD PO</td>
<td>75 mg / daily PO</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>10 mg / BD inhalations</td>
<td>10 mg / daily inhalations</td>
</tr>
<tr>
<td>Peramivir</td>
<td>600 / mg /BD / IV</td>
<td>600 / mg /d / IV</td>
</tr>
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</table>
Patients with severe disease

- For patients with severe or complicated illness with suspected or confirmed influenza who are not hospitalized, antiviral treatment with oral or enterically-administered oseltamivir is recommended as soon as possible.

- There are insufficient data for inhaled zanamivir and intravenous peramivir in patients with severe influenza disease.

- There are no available data from clinical trials on use of baloxavir treatment in patients with severe influenza disease.
Duration of antiviral treatment

- The optimal duration and dosing of antiviral treatment are uncertain for *severe or complicated influenza*.

- **Treatment regimens might need to be altered** to fit the clinical circumstances. For example, clinical judgment should be the guide regarding the need to extend daily treatment regimens **longer than 5 days** for patients whose **illness is prolonged**. **Critically ill patients** with respiratory failure can have prolonged influenza viral replication in the lower respiratory tract and might benefit from longer duration of treatment.
Longer antiviral treatment

- Longer treatment regimens might be necessary in immunosuppressed people who may have prolonged influenza viral replication.

- Such patients are at risk of emergence of influenza viruses with antiviral resistance during or after antiviral treatment.

- A higher dose of oral or enterically-administered oseltamivir has been recommended by some experts (e.g., 150 mg twice daily in adults with normal renal function) for treatment of influenza in immunocompromised patients and in severely ill hospitalized patients.
For patients who cannot tolerate or absorb oral or enterically-administered oseltamivir because of suspected or known gastric stasis, malabsorption, or gastrointestinal bleeding, the use of intravenous peramivir should be considered.
emergence of antiviral resistant viruses

- It is possible that some influenza viruses may become less susceptible or resistant to oseltamivir and peramivir during antiviral treatment with one of these drugs and remain susceptible to zanamivir.
- This has been reported most often for influenza A(H1N1).
- Severely immunosuppressed people (e.g., HSCT recipients) are at highest risk for emergence of antiviral-resistant influenza virus infection during or following oseltamivir and/or peramivir treatment.
- Resistance and reduced susceptibility of influenza viruses to antiviral drugs can also occur spontaneously, with no known exposure to antiviral medications.
Chemoprophylaxis

- Recommended duration is 7 days (after last known exposure).

- For control of outbreaks in institutional settings (e.g., long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis with oral oseltamivir or inhaled zanamivir for a minimum of 2 weeks and continuing up to 1 week after the last known case was identified.

- Baloxavir is approved for post-exposure prophylaxis (single-dose) of influenza in persons aged 12 years and older.”
Routine use of post-exposure chemoprophylaxis is not recommended; one reason for this is to avoid sub-therapeutic treatment dosing if infection is already established, although the likelihood of emergence of antiviral resistant viruses is unknown.

Antiviral chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the first exposure to a person with influenza.
**chemoprophylaxis**

- CDC does not recommend to use oseltamivir generally for prevention due to concerns that widespread use will encourage resistance development.
- It should be considered in those at high risk, who have been exposed to influenza within 48 hours and have not received or only recently been vaccinated (during the first two weeks following vaccination).
- They recommended it during outbreaks in long term care facilities and in those who are significantly immunosuppressed who might not respond to influenza vaccination.
Drug interactions

- Concurrent administration of antiviral drugs with intranasal live attenuated influenza vaccine (LAIV) may inhibit viral replication of LAIV and thereby decrease the effectiveness of LAIV vaccination.

  - **LAI should not be given if:**
    - oseltamivir or zanamivir was administered within 48 hours
    - or if peramivir was administered within 5 days of planned vaccination,
    - or if baloxavir was administered within 17 days of planned vaccination.

- If LAIV is given, and antiviral medications are subsequently administered up to two weeks after vaccination, **LAIV should be revaccinated with another appropriate influenza vaccine.**
Passive immunity

- **Transfused antibodies**
- An alternative to vaccination used in the [1918 flu pandemic](https://en.wikipedia.org/wiki/1918_flu_pandemic) was the direct transfusion of blood, plasma, or serum from recovered patients. Eight publications reported that the treatment could approximately halve the mortality in hospitalized severe cases with an average case-fatality rate of 37% when untreated.

- **Ex vivo culture of T lymphocytes**
- Human [T lymphocytes](https://en.wikipedia.org/wiki/Lymphocyte) can be expanded in vitro. [Clonal populations](https://en.wikipedia.org/wiki/Clonal_selection) of [CD8+ cytotoxic T cells](https://en.wikipedia.org/wiki/CD8) have been grown which carry [T cell receptors](https://en.wikipedia.org/wiki/T-cell_receptor) specific to influenza. These work much like [antibodies](https://en.wikipedia.org/wiki/Antibody) but are permanently bound to these cells. This method is still in early research.
Thanks for your attention!