Pharmacological treatment and prophylaxis of influenza

Version 1.2  17 December 2010
Summary
This guidance summarises the current HPA recommendations for the antiviral treatment and prophylaxis of influenza. The summary draws on guidance issued by the National Institute for Health and Clinical Excellence1,2, the Department of Health3 and the World Health Organization4,5. In areas where guidance or evidence from adequate randomized controlled trials is absent, the therapeutic recommendations rely on expert opinion and current consensus. The document uses typical scenarios that may be encountered in clinical practice to illustrate the specific recommendations for the administration of antiviral drugs, including the emergence of antiviral resistance, and contains a flow chart to assist decision making.

Background
The clinical features of human infection with influenza virus may range from asymptomatic infection, mild typical influenza mainly affecting the upper respiratory tract to progressive or complicated influenza involving a critical illness with multi-organ dysfunction, bacterial super-infection or exacerbation of underlying medical conditions.

Antiviral therapy may be beneficial in human influenza and has been associated with prevention of disease or complications among patients exposed to the virus, shortened duration of illness among acutely-ill patients and reduction of morbidity and mortality among patients with severe infection6.

General Considerations
1. In the event of the emergence of a novel influenza strain this advisory will require review.
2. Influenza vaccination and infection control practices are of utmost importance in preventing infection and are universally preferred over the administration of chemoprophylaxis.
3. Antivirals should be used in accordance with NICE guidance (as amended to include pregnant women in the at-risk groups) and can only be prescribed in primary care once the surveillance systems have indicated that flu is circulating in the community. Cases in hospital can be treated with antivirals if influenza is suspected at any time.
4. Once flu is circulating in the community, people with flu-like illness in at-risk groups should be started on antivirals by primary care as soon as possible. In the community these should be given within 48 hours of onset of symptoms, in a hospitalised patient antivirals can be given beyond the 48 hour period.
5. The choice and route of administration of antiviral drug therapy should be guided by host risk factors and clinical condition.
6. A high index of suspicion should be maintained for diagnosing antiviral resistant influenza, especially among immunocompromised patients, patients with treatment failure or progressive infection despite adequate therapy or contacts of individuals known to be infected with resistant strains. The choice of antiviral agent for empiric therapy should be guided by the likelihood of antiviral resistance based on current epidemiological and virological data (figure 1); in general, most H1N1 (2009) influenza and non-pandemic zoonotic, H3N2 or influenza B strains are susceptible to oseltamivir. Pre-pandemic influenza A (H1N1) is commonly resistant to oseltamivir but likely to be susceptible to M2 channel inhibitors and zanamivir (Table 1).
7. Adequate dose, dosing interval and duration of antiviral therapy reduce the likelihood of emergence of resistance during therapy.
8. In certain clinical situations, sequential monitoring of virus shedding may aid in determining the duration of antiviral chemoprophylaxis or therapy.
The properties of the major antiviral drugs

The properties of the major antiviral drugs are summarised in Table 1.

**Table 1: Features of antiviral drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Typical adult dosage¹</th>
<th>Side effects</th>
<th>Resistance profile</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Neuraminidase inhibition</td>
<td>75 mg bd for 5 days (See ¹,²)</td>
<td>GI disturbances. Rarely hepatitis, arrhythmia and Stevens-Johnson</td>
<td>Uncommon H275Y mutation in H1N1 strains</td>
<td>Dose reduction in renal failure³ Pregnancy category C⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 mg Daily for 10 days</td>
<td></td>
<td>More rare mutations in other subtypes</td>
<td></td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Neuraminidase inhibition</td>
<td>10 mg bd for 5 days</td>
<td>Rarely bronchospasm or angioedema</td>
<td>Rare. I223R detected in ~10 cases of H1N1 (2009) worldwide.</td>
<td>Pregnancy category C Can be given via i.v. route</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10mg daily for 10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peramivir (Unlicensed)</td>
<td>Neuraminidase inhibition</td>
<td>600 mg i.v. qd for 5-10 days</td>
<td>GI disturbances, psychiatric abnormalities, neutropenia</td>
<td>Rare. H275Y mutation reduces efficacy.</td>
<td>Dose reduction in renal failure. Unlicensed drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine (rarely used in the UK)</td>
<td>M2 channel inhibitor</td>
<td>100 mg daily for 5 days</td>
<td>Confusion, insomnia, exacerbation of underlying neurological conditions</td>
<td>Common. H1N1 (2009) 100% resistant Varying rates in H3N2 / seasonal H1N1 / influenza B</td>
<td>Dose reduction in renal failure. Pregnancy category C⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg daily (duration variable)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Paediatric dosages: oseltamivir – 2.5 mg/kg bd for children 1-3 months, 3.0 mg/kg for children 3-12 months. For 1-13 years the recommended oseltamivir dose is 30 mg, 45 mg, 60 mg or 75 mg bd for children weighing <15 kg, 15-23 kg, 23-40 kg or >40 kg, respectively. For those over 13 years the dose is the same as adults. For infants and young children, oseltamivir oral suspension is preferred. Zanamivir dosage (> 5 years) same as for adults.
2. Doses of up to 150mg bd and duration up to 10 days have been administered compassionately to critically-ill patients.
3. Inhaled zanamivir should be considered in patients with severe renal failure.
4. Some authorities prefer inhaled zanamivir for pregnant women because of reduced systemic exposure. However, this is not supported by evidence and oseltamivir is not contra-indicated in pregnancy.
5. M2 channel inhibitors should not be administered to pregnant women or young children with uncomplicated illness.

**Definitions**

1. **Uncomplicated influenza** – an influenza-like illness manifesting as fever (in the majority of patients), upper respiratory tract symptoms (cough, sore throat, rhinorrhea), generalized symptoms (headache, malaise, myalgia, arthralgia) and GI symptoms, without evidence of target-organ involvement.
2. **Complicated influenza** – an influenza-like illness requiring hospital admission and/or presenting with symptoms and signs of lower respiratory tract infection (hypoxemia, dyspnea, lung infiltrate), central nervous system involvement (altered mentation,
encephalitis) or other form of target-organ damage and/or a significant exacerbation of an underlying medical condition (such as cardiac, hepatic, pulmonary or renal insufficiency or diabetes mellitus).

3. **Progressive influenza** – progression from uncomplicated influenza to complicated influenza.

4. **Risk factors for complicated or progressive influenza** – host factors associated with a significantly increased risk for complicated or progressive disease, including pregnancy (especially in 3rd trimester and up to 2 weeks post-partum), children <2 years, adults >65 years, chronic cardiac, pulmonary, renal or hepatic insufficiency, diabetes mellitus, debilitating neurological conditions and primary or secondary immunosuppression.

5. **Prophylaxis** – low-dose antiviral therapy administered for the prevention of influenza. Prophylaxis is usually given post-exposure. Full-dose antiviral therapy may be administered to certain immunocompromised individuals due to increased likelihood of emergence of resistance during therapy.

6. **Standard therapy** – antiviral therapy administered for suspected or proven clinical influenza.

**Recommendations for Treatment and Prophylaxis of Influenza**

**Clinical illness**
An algorithm for treatment considerations during clinical illness due to influenza is given in figure 2.

**Scenario 1 - Uncomplicated influenza in otherwise healthy individuals.**
1. Otherwise healthy individuals with suspected or proven influenza do not need antiviral therapy.
2. Pregnant women are considered to be at-risk (see scenario 2).
3. Patients should be informed about the symptoms and signs of complicated influenza and instructed to seek medical attention if these occur.
4. Patients should be advised to self-isolate until symptom free.

**Scenario 2 – Uncomplicated influenza among high-risk individuals.**
1. All high-risk individuals, including pregnant women, with suspected or proven influenza should be offered antiviral therapy if treatment can be started within 48 hours (36 hours for Zanamivir treatment in children) of the onset of symptoms.
2. Treatment should commence as early as possible.
3. Therapy should be given empirically and not deferred until laboratory test results are known.
4. With the exception of severely immunocompromised patients, the drug of choice for high-risk patients is oseltamivir at standard dosage and duration.
5. There is no evidence to support the use of inhaled zanamivir instead of oseltamivir in pregnant women and both zanamivir and oseltamivir may be administered to pregnant women.
6. Severely immunocompromised patients should be given inhaled zanamivir at a standard dose for 10 days.
7. If oseltamivir resistance is known or suspected on clinical or epidemiological grounds, inhaled zanamivir should be administered.
8. If oseltamivir resistance is likely according to epidemiological and virological data, inhaled zanamivir prophylaxis should be administered.

9. There is insufficient evidence to indicate dual neuraminidase inhibitor therapy.

10. Patients should be informed regarding symptoms and signs of complicated influenza and instructed to seek medical attention in such an occurrence.

11. Patients should be advised to self-isolate until symptom free.

Scenario 3 - Complicated or progressive clinical illness.
1. All patients with complicated or progressive influenza, including children at all ages, should be treated with antiviral drugs, regardless of risk factors and immune status.

2. Treatment should commence as early as possible.

3. Therapy should be given empirically and not deferred until laboratory test results are known.

4. The drug of choice is oseltamivir at standard dosage and duration.

5. Higher doses and longer duration of oseltamivir may be considered in critically-ill patients.

6. Antiviral susceptibility should be tested in patients failing to improve after 5 days of therapy.

7. In critically-ill patients and patients with impending respiratory failure, intravenous zanamivir is preferred over inhaled zanamivir.

8. Immunocompromised patients should be given inhaled zanamivir therapy regardless of antiviral susceptibility. Therapy should be continued until viral shedding from the respiratory tract is not evident in sequential samples.

9. If oseltamivir resistance is known or suspected on clinical or epidemiological grounds, inhaled zanamivir should be administered at standard dose for 5-10 days.

10. If oseltamivir resistance is likely according to epidemiological and virological data, inhaled zanamivir prophylaxis should be administered.

11. Shedding of resistant virus should be monitored for infection control purposes until no longer detected to limit or avoid exposure of vulnerable patients.

12. In all cases, strict infection control measures should be instituted, until viral shedding is not evident upon sequential testing.

13. Peramivir may be considered a last-line alternative to zanamivir if the latter drug is unavailable.

14. Experimental therapeutic agents such as parenteral oseltamivir, intravenous immunoglobulins (IVIG) or novel antiviral agents (e.g. laninavir) should be considered for last-line compassionate use in unique cases.

Scenario 4 – New detection of antiviral resistance in patients with uncomplicated influenza already treated with oseltamivir.
1. Oseltamivir therapy should be stopped. Any further therapeutic decisions should be guided by the patient’s condition.

2. Patients who are well or recovering need not receive alternative antiviral therapy.

3. Patients who are symptomatic should be switched to inhaled zanamivir at a standard dose for 5-10 days.

4. Patients with complicated or progressive clinical illness should be treated as below.

5. Shedding of resistant virus should be monitored for infection control purposes.
6. In all cases, strict infection control measures should be instituted, preferably until viral shedding is not evident upon sequential testing.

**Prophyalxis**

An algorithm for treatment considerations following exposure to influenza is given in figure 3.

**Scenario 5 – Possible exposure of otherwise healthy individuals to patients with influenza**

1. Onward transmission of influenza should be minimised by institution of strict infection control measures.

2. Chemoprophylaxis is not recommended for otherwise healthy individuals in the setting of potential exposure to infected patients or following exposure, regardless of the source’s antiviral susceptibility.

3. Patients should be informed regarding symptoms and signs of influenza and instructed to seek medical attention in such an occurrence.

4. Prophylaxis may be considered by health protection professionals in institutional or other special settings where continuous or repeated exposure is evident.

**Scenario 6 – Possible exposure of individuals with risk factors for influenza to patients with influenza**

1. Onward transmission of influenza should be minimized by institution of strict infection control measures.

2. Chemoprophylaxis with an antiviral should be offered to individuals with risk factors for influenza who have been exposed to a patient with influenza if, antivirals can be started within 48 hours of last contact for oseltamivir or 36 hours for zanamivir. Close patient monitoring and prompt diagnosis and treatment of influenza are an alternative.

3. The drug of choice is oseltamivir at standard dosage for prophylaxis for 10 days.

4. If oseltamivir resistance is known or suspected among contacts on clinical or epidemiological grounds, inhaled zanamivir prophylaxis should be administered for 10 days.

5. If oseltamivir resistance is likely according to epidemiological and virological data, inhaled zanamivir prophylaxis should be administered for 10 days.

6. There is no evidence to support the use of inhaled zanamivir instead of oseltamivir in pregnant women and both zanamivir and oseltamivir may be administered to pregnant women.

**Scenario 7 – Possible exposure of immunocompromised individuals to patients with influenza**

1. Onward transmission of influenza should be minimized by institution of strict infection control measures.

2. Chemoprophylaxis should be offered to immunocompromised patients who have been exposed to infected patients as in Scenario 6.

3. In light of the high risk for the development of oseltamivir resistance among H1N1 (2009) strains, full-dose inhaled zanamivir should be offered as chemoprophylaxis in immunocompromised individuals, regardless of the source’s antiviral susceptibility.

4. The risk for emergence of such mutations among H3N2 viruses is unknown and therefore the relative frequency of circulating H3N2 and H1N1 (2009) might need to be considered.
Figure 1: Likelihood of oseltamivir resistance

One or more of the following is currently the dominant circulating strain:
- Pandemic (H1N1) 2009
- Influenza B
- Influenza A (H3N2)
- Other zoonotic influenza A

Oseltamivir resistance unlikely

Consult a clinical virologist

One or more of the following conditions:
- Seasonal Influenza A (H1N1) is dominant or co-dominant
- Rapid spread of a novel mutation
- Emergence of a novel resistant strain
- Prevalence of resistance among Pandemic (H1N1) 2009 >10%

Oseltamivir resistance likely
Figure 2: Choice of antiviral therapy for influenza-like illness

Antiviral generally not indicated

High-risk individual?

Immuno-compromised?

Oseltamivir resistance known or suspected among contacts?

Oseltamivir resistance likely?

Pregnancy?

Oral oseltamivir

Individuals presents with influenza-like illness

Complicated influenza?

Oseltamivir (or high-dose oseltamivir)

Critical illness?

Immuno-compromised?

Oseltamivir resistance known or suspected among contacts?

Oseltamivir resistance likely?

Pregnancy?

Oral oseltamivir or oral oseltamivir

Inhaled zanamivir

Inhaled zanamivir

Inhaled zanamivir

Inhaled zanamivir

Inhaled zanamivir

Inhaled zanamivir

Inhaled zanamivir

Inhaled zanamivir

Inhaled zanamivir
Figure 3: Choice of antiviral prophylaxis following exposure

- **Individuals presents following exposure to influenza-like illness**
  - Risk factors for complicated flu?
    - Yes → Immuno-compromised?
      - Yes → Antivirals should be strongly considered
      - No → Antivirals should be considered
    - No → Antiviral generally not indicated
  - No → Immuno-compromised?
    - Yes → Antivirals should be strongly considered
    - No → Antivirals should be considered

- Antivirals should be considered
  - Oseltamivir resistance known or suspected among contacts?
    - Yes → Inhaled zanamivir
    - No → Oseltamivir resistance likely?
      - Yes → Inhaled zanamivir
      - No → Pregnancy?
        - Yes → Inhaled zanamivir or oral oseltamivir
        - No → Oral oseltamivir
References

2. TA158 Oseltamivir, amantadine (review) and zanamivir for the prophylaxis of influenza; review of NICE technology appraisal guidance 67. September 2008 Available at: http://guidance.nice.org.uk/TA158