

8.1 Introduction

Initial management will depend on the assessment of the reason for admission, the presence of complications, and the impact of the influenza on any pre-existing disease, or psychosocial factors. For instance, some elderly patients may require admission for social reasons.

In broad terms, the most likely clinical reasons for admission will be (in order of frequency):

Lower respiratory tract complications

- Non pneumonic bacterial exacerbation of chronic lung disease such as COPD (possibly with a mixed viral infection)
- Secondary bacterial pneumonia
- Mixed bacterial and viral pneumonia
- Primary viral pneumonia

Cardiac complications

- Exacerbation of pre-existing cardiac disease with cardiac failure and/or arrhythmia
- Primary myocarditis

Other complications

- Exacerbation of other pre-existing disease, such as diabetes mellitus
- Neurological complications
- Rhabdomyolysis
- Severe sinusitis

The initial management is likely to most usually involve that of respiratory and cardiac complications, especially pneumonia and these are discussed below. Management of other less common primary influenzal complications (such as rhabdomyolysis, encephalopathy) is not covered.

8.2 What initial management strategy should be offered to patients with respiratory and cardiac complications?

All influenza patients admitted to hospital with abnormal cardiorespiratory symptoms and signs, including influenza-related pneumonia should have a chest radiograph, and electrocardiogram and should have oxygenation assessed by pulse oximetry, preferably whilst breathing air (see Section 6). Those with $\text{SaO}_2 < 92\%$ should have arterial blood gas measurements, as should all patients with features of severe illness. Knowledge of the inspired oxygen concentration is essential to the interpretation of blood gas measurements and should be clearly recorded with the blood gas result.

Continuous oxygen therapy is indicated for those patients with $\text{PaO}_2 < 8$ Kpa, hypotension with systolic BP < 100 mmHg, metabolic acidosis with bicarbonate < 18 mmol/l or respiratory distress with respiratory rate $> 30/\text{min}$.⁽⁶²⁾ The aim of oxygen therapy should be to maintain PaO_2 at > 8 Kpa or $\text{SaO}_2 > 92\%$. Unless complicated by severe chronic obstructive pulmonary disease with ventilatory failure, high concentrations of oxygen of 35% or greater are indicated and can be safely used.

High concentration oxygen therapy given to patients with pre-existing chronic obstructive pulmonary disease who may have CO₂ retention can reduce hypoxic drive and increase ventilation-perfusion mismatching. In such patients initial treatment with low oxygen concentrations (24-28%) should be progressively increased on the basis of repeated arterial blood gas measurements, the aim being to keep PaO₂ >6.65 Kpa without causing a fall in arterial pH below 7.26,(63) in line with the management strategy recommended in the NICE COPD Guidelines(58). Non-invasive ventilation (NIV) may often be of value. Non-invasive ventilation in patients with pneumonia but without co-existing COPD has not been shown to influence mortality. The use of NIV in such patients should not delay the institution of invasive ventilation if appropriate.(59;64)

Patients should be assessed for volume depletion and may require IV fluids. The potential for influenza to cause cardiac decompensation, either through exacerbation of pre-existing cardiac disease or from a primary myocarditis should be borne in mind, with any complicating heart failure and arrhythmias being managed in the usual way.

Physiotherapy may be of benefit in selected patients with excess bronchial secretions, particularly those with concurrent chronic obstructive pulmonary disease. In cases of severe illness requiring prolonged hospital admission, increased nutritional support whether enteral, parenteral or via naso-gastric feeding should be arranged.

Recommendations

- Hypoxic patients should receive appropriate oxygen therapy with monitoring of oxygen saturations and inspired oxygen concentration with the aim to maintain PaO₂ ≥8 Kpa and SaO₂ ≥92%. High concentrations of oxygen can safely be given in uncomplicated pneumonia.
- Oxygen therapy in patients with pre-existing chronic obstructive pulmonary disease complicated by ventilatory failure should be guided by repeated arterial blood gas measurements. Non invasive ventilation may be helpful.
- Patients should be assessed for cardiac complications and also volume depletion and their need for additional intravenous fluids.
- Nutritional support should be given in severe or prolonged illness.

8.3 What monitoring should be conducted during hospital stay?

Pulse, blood pressure, respiratory rate, temperature, oxygen saturation (with a recording of the inspired oxygen concentration at the same time) and mental status should be measured initially at least twice daily. This is most conveniently performed using an Early Warning Score (EWS) chart, which all ward staff should be familiar with. Those with severe illness, requiring continuous oxygen or cardiovascular support, should be monitored more frequently.

Failure to improve clinically within 48 hours should result in a full clinical reassessment and failure to improve over 4 days is an indication to repeat the chest radiograph.

Recommendations

- Temperature, respiratory rate, pulse, blood pressure, mental status, oxygen saturation and inspired oxygen concentration should be monitored and recorded initially at least twice daily and more frequently in those with severe illness or requiring regular oxygen therapy.
- An Early Warning Score system is a convenient way to perform this.
- In addition to a full clinical reassessment, a chest radiograph should be repeated in patients who are not progressing satisfactorily.

8.4 When can patients be safely discharged from hospital?

There will be considerable pressure to discharge patients early during a pandemic. The type and availability of out-of-hospital facilities will dictate hospital discharge decisions. Some guidance regarding simple parameters to review when considering hospital discharge can be obtained from a recent US prospective, multi-centre, observational cohort study of 680 patients admitted to hospital with CAP(65) and are offered as advice for all patients admitted with influenza-related respiratory complications.

Recommendations

- **Patients should be reviewed before 24 hours of discharge home. Those with more than 2 of the following unstable clinical factors should consider remaining in hospital:**
 - a. **temperature > 37.8°C**
 - b. **heart rate > 100/min**
 - c. **respiratory rate > 24/min**
 - d. **systolic blood pressure <90mmHg**
 - e. **oxygen saturation < 90%**
 - f. **inability to maintain oral intake and abnormal mental status.**

8.5 What arrangements should be made for follow up after hospital discharge for influenza and by whom?

It is usual practice to arrange "routine" hospital clinic follow up and repeat the chest radiograph at around 6 weeks after discharge for acute respiratory illness such as pneumonia. However, there is no evidence on which to base a recommendation regarding the value of this practice in patients who have otherwise recovered satisfactorily. It is also not known whether there is any value in arranging clinical follow up in a hospital clinic rather than with the patient's general practitioner. During an influenza pandemic situation, it is likely that only patients who developed complications or who had significant worsening of their underlying disease will be offered clinical review at one or other venue.

At discharge, patients should be offered access to information about their take home medication, smoking and lifestyle advice as appropriate, potential future complications and action to take in the event of a relapse of symptoms.

Recommendations

- **Follow up clinical review should be considered for all patients who suffered significant complications or who had significant worsening of their underlying disease, either with their general practitioner or in a hospital clinic.**
- **At discharge or at follow up, patients should be offered access to information about their illness, take home medication and any followup arrangements.**
- **It is the responsibility of the hospital team to arrange the follow up plan with the patient and the general practitioner.**

9.1 What drugs should be used for antiviral treatment during a pandemic?

Oseltamivir (neuraminidase inhibitor) will be the mainstay for therapy in the pandemic. The M2 inhibitors, amantadine and rimantadine, are unsuitable for use for *treatment* due to the rapid emergence of resistance together with side-effects.

From clinical trial data accrued to date and based on seasonal, interpandemic influenza, the *anticipated* positive effect of antivirals in a pandemic will be:

- (a) reduction of illness duration by 24 hours, and therefore more rapid mobilisation of affected individuals including essential workers
- (b) a possible reduction in hospitalisation of infected individuals
- (c) a reduction of subsequent antibiotic use by infected individuals

The evidence accrued to date does not suggest there will be a reduction of overall mortality. Therefore the major utility of antivirals will be to maintain the essential workforce, and reduce hospitalisation and antibiotic treatment of complications.

9.2 Who should be treated with antivirals (neuraminidase inhibitors) during a pandemic?

Recommendations

- **Individuals should only be considered for treatment with neuraminidase inhibitors if they have all of the following:**
 1. an acute influenza-like illness
 2. fever (>38°C) *and*
 3. been symptomatic for 2 days or less
- **Treatment Schedule: Adults: Oseltamivir 75mg every 12 hours for 5 days. Dose to be reduced by 50% if creatinine clearance is less than 30ml/minute.**
- **EXCEPTIONS:**
 - a) **Patients who are unable to mount an adequate febrile response eg. the immunocompromised or very elderly, may still be eligible despite lack of documented fever.**
 - b) **Hospitalised patients who are severely ill, particularly if also immunocompromised, may benefit from antiviral treatment started more than 48 hours from disease onset. (This advice reflects the lack of robust evidence to guide the use of antivirals in such patients and places a high value on the potential benefits of antiviral therapy.)**

9.3 Delivery of antivirals in Primary Care.

National distribution arrangements are laid out in the UK Operational Framework for stockpiling, distributing and using antiviral drugs in the event of pandemic influenza.(3) The drug will be made available through these arrangements to pharmacies, PCTs and/or GP surgeries.

Recommendations

- PCTs are encouraged to plan for the delivery of antivirals to the large numbers of previously healthy persons with an ILI via community health professionals, including community pharmacists.
- GPs should focus their efforts on assessment and management of those persons at high risk of complications (see Appendix 2) and patients developing complications.

9.4 How do antivirals work?

Drugs available for treatment and prevention of infection by influenza are summarised in Table 9.1. There are four drugs available, the older agents, amantadine and rimantadine, and the neuraminidase inhibitors, oseltamivir and zanamivir.

Older Agents: The older agents, amantadine and rimantadine (rimantadine is not currently licensed in the UK), are related substances that act by blocking the ion-channel function of the influenza virus M2 protein. This protein, although a minor surface constituent of the influenza virus particles, is essential for virus replication. They are only active against influenza Type A. Amantadine is not recommended by NICE for treatment and/or prophylaxis of inter-pandemic influenza, so in the absence of national stockpiling, supplies of amantadine can be expected to be very low. H5 viruses in SE Asia are resistant to amantadine, so may play no role at all depending on the nature of the pandemic strain.

Neuraminidase inhibitors: Neuraminidase inhibitors have been developed that have a potent anti-influenza activity *in vitro* and also have clinical efficacy. They are active against both Type A and Type B influenza viruses. The neuraminidase (NA) surface protein of the virus is essential for the de-aggregation and release of newly synthesized virions from infected cells. Inhibition of this enzyme interrupts propagation of the influenza virus within the human respiratory tract.

Two neuraminidase inhibitors so far have been developed to the level of entry into the formulary:

- Zanamivir is a modification of Neu5Ac2en, a dehydrated neuraminic acid derivative.
- Oseltamivir is a similar molecule except it has a cyclohexene ring and replaces a polyglycerol moiety with lipophilic sidechains.

Oseltamivir can be taken by mouth, whereas Zanamivir must be inhaled, using a Diskhaler device. An intravenous formulation of zanamivir has been developed but its efficacy has not been established. This may be relevant for the management of ventilator cases. Both drugs are active against both the influenza Type A and influenza Type B viruses.

9.5 What effect do antivirals have on the natural history of influenza?

Older agents: Both amantadine and rimantadine are effective for the treatment of Type A influenza virus infection if treatment is begun within 48 hours of the onset of illness. (66) Historical data show that they can shorten the illness by approximately one day but their efficacy or in preventing complications, hospitalisations, or deaths has never been established. Although these drugs are effective, their use in clinical influenza treatment has been limited as a result of their proclivity to induce viral resistance, and their side-effect profile.

Neuraminidase inhibitors:

9.5.1 Effect on symptoms

Several large clinical trials have demonstrated the utility of zanamivir and oseltamivir in treatment of adults with influenza in the community (Table 9.2). The evidence yielded by these studies has recently been reviewed by the Cochrane Collaboration.(67) Overall, neuraminidase inhibitors have been shown to shorten the duration of symptoms by one day. Across all studies, the time gained in returning to normal activities is half a day for laboratory-confirmed cases of influenza. The beneficial effect appears to be confined to patients in whom there is fever, (38°C in the study reported by Nicholson et al, 2000 (68), and 37.8°C in the study reported by the MIST group 1998(69)) and who are treated within 48 hours of the onset of symptoms. Oseltamivir has also been shown to have efficacy in children aged 1-12 years. In one study involving 452 children with proven influenza the median duration of illness was reduced by 36 h (26%) in oseltamivir compared with placebo recipients (101 h, 95% confidence interval, 89 to 118 vs. 137 h; 95% confidence interval, 125 to 150; $P < 0.0001$). Oseltamivir treatment also reduced cough, coryza and duration of fever (70) The neuraminidase inhibitors may have the additional benefit of reducing transmission between hosts; in studies of experimental human influenza, zanamivir greatly reduced titres of virus cultured from the nasopharynx as well as the mean duration of viral shedding (71)

9.5.2 Effect on outcomes

Virtually all studies on the efficacy of neuraminidase inhibitors to reduce complications have been conducted with oseltamivir, and this drug has been shown to have some effect on outcomes other than time to recovery. In a metanalysis of adults and adolescents with a virologically proven influenza illness, oseltamivir treatment reduced overall antibiotic use for any reason by 26.7% (14.0% vs 19.1% with placebo; $P < .001$) and the incidence of influenza-related chest infections such as bronchitis resulting in antibiotic therapy by 55% (4.6% vs 10.3% with placebo; $P < .001$). In those subjects considered at increased risk of complications, 74 (18.5%) of 401 placebo recipients developed a chest infection leading to antibiotic use compared with 45 (12.2%) of 368 oseltamivir recipients (34.0% reduction; $P = .02$). Hospitalization for any cause occurred in 18 (1.7%) of 1063 placebo recipients compared with 9 (0.7%) of 1350 oseltamivir-treated patients (59% reduction; $P = .02$). In contrast, among subjects with an influenza-like illness but without a confirmed influenza infection, the incidence of complicating chest infections (6.7% vs 5.3%), overall antibiotic use (19.7% vs 19.3%), or hospitalizations (1.7% vs 1.9%) was similar between placebo and oseltamivir recipients, respectively. (72) In a study of children aged 1-12 with proven influenza, children with proven, new diagnoses of otitis media arising as a complication of influenza were reduced by 44% (12% vs. 21%). The incidence of physician-prescribed antibiotics was significantly lower in influenza-infected oseltamivir (68 of 217, 31%) than placebo (97 of 235, 41%; $P = 0.03$) recipients.(70) So far, the neuraminidase inhibitors have not been extensively investigated in patients who are at the highest risk of serious complications of influenza. Such patients include the elderly and those with serious cardiopulmonary illness, such as chronic obstructive pulmonary disease. The neuraminidase inhibitors have not been associated with a reduction in mortality, but the clinical trials conducted so far have not been appropriate to measure this.

9.6 Will antivirals have activity against the pandemic strain of influenza virus?

It is not known for certain whether the neuraminidase inhibitors will be effective in pandemic influenza because their use has only been assessed in inter-pandemic influenza, where the virulence is moderate and there is some degree of host immunity. The antiviral activity is likely to be adequate; *in vitro*, all neuraminidase inhibitors have been demonstrated to have a broad spectrum of activity against multiple avian influenza viruses.(73) The older agents, rimantadine and amantadine, were studied in both the 1968 Hong Kong pandemic and again when H1N1 influenza appeared in a pandemic in 1977. Their efficacy has been reviewed by Hayden.(66) When the older agents were given for 4-8 week periods *as prophylaxis* in a community setting, their protective efficacy against influenza illness averaged 70% compared

with placebo. This compares with 80-90% efficacy observed with the same agents in studies during the interpandemic period.

9.7 Can influenza virus develop resistance to the antivirals?

When amantadine or rimantadine are used to treat patients, resistant viruses emerge rapidly and approximately 30% of treated children or adults will shed resistant variants starting 2-5 days after the onset of treatment.(71) The resistant viruses shed from these patients retain full virulence, infectivity and transmission potential. When contacts of cases treated with amantadine or rimantadine are given post-exposure prophylaxis with these older agents, the reduction in secondary cases is minimal.(74)

In contrast the frequency of emergence of resistance during treatment with the neuraminidase inhibitors is reported to be low. However, during studies of experimentally-induced influenza A/H1N1 infection in healthy adults, 4% of participants shed viruses with a histidine to tyrosine substitution at position 274 within the binding site of oseltamivir.(75) In these cases the volunteers had increased influenza viral load within the nasopharynx but there was no deterioration of symptoms. So far, there have been no proven instances of transmission of oseltamivir or zanamivir-resistant variants in field clinical trials, but the experience is relatively small currently. Sequence analysis of H5N1 human isolates from North Vietnam have revealed virus with a 274-Y (resistant) sequence. Although the isolate was not fully resistant, its IC50 for oseltamivir was shifted upwards and it is therefore less susceptible to oseltamivir than other H5N1 isolates that had been tested from the region. The patient from whom the virus was isolated was concurrently being treated with oseltamivir.

9.8 What side-effects occur during use of antivirals?

Both amantadine and rimantadine can cause nausea and vomiting in a small percentage of individuals receiving them (Table 9.1). Unfortunately amantadine is also associated with very unpleasant central nervous system side-effects including anxiety, depression, insomnia and hallucinations. The side-effects are dose-related and do resolve with discontinuation of the drug. In the case of the neuraminidase inhibitors, both drugs appear relatively safe. Zanamivir has very few side-effects, but can result in bronchospasm which might be potentially serious in patients with asthma. Oseltamivir, requires dose-reduction in patients with low creatinine clearance (< 30ml/min). Nausea occurs in 5-15% of oseltamivir recipients but is seldom severe enough to lead to drug discontinuation.

Table 9.3: Side-effects of oseltamivir

Main side-effects	Nausea, vomiting, abdominal pain, dyspepsia, diarrhoea, headache, fatigue, insomnia, dizziness, conjunctivitis, nose-bleed, rash, ear disorders
Rare side-effects	Hypersensitivity reactions
Very rare side-effects	Hepatitis, Stevens-Johnson syndrome