Influenza - Guidelines for the Intensive Care Unit 2010

Summary These guidelines provide direction to intensive care units in NSW public hospitals regarding management of patients with influenza-like illness in the intensive care unit for the 2010 influenza season.

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Distributed to Public Health System, NSW Ambulance Service, Ministry of Health, Private Hospitals and Day Procedure Centres
Audience All staff in intensive care units; infectious disease physicians; clinical microbiologists

Secretary, NSW Health
This Policy Directive may be varied, withdrawn or replaced at any time. Compliance with this directive is mandatory for NSW Health and is a condition of subsidy for public health organisations.
INFLUENZA - GUIDELINES FOR THE INTENSIVE CARE UNIT - 2010

PURPOSE
These guidelines provide recommendations for intensive care units in NSW public hospitals regarding management of patients with influenza-like illness in the intensive care unit for the 2010 influenza season.

KEY PRINCIPLES
The guidelines include information about the influenza virus, clinical management of patients with influenza-like illness, and laboratory testing for influenza.

Guidance is provided for treatment, laboratory testing and infection control for patients with influenza-like illness in the intensive care unit in 2010 (Appendix 1).

USE OF THE GUIDELINE
Intensive care units in public hospitals should consider the information in these guidelines for management of patients with influenza-like illness in 2010. Intensive care units in private hospitals may also find the guidelines useful.

REVISION HISTORY

<table>
<thead>
<tr>
<th>Version</th>
<th>Approved by</th>
<th>Amendment notes</th>
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<tbody>
<tr>
<td>May 2010 (GL2010_005)</td>
<td>Deputy Director- General Population Health</td>
<td>New guideline that supercedes the document Influenza in the Intensive Care Unit v2.0, 5 August 2009, that was not formally issued as a NSW Health Guideline</td>
</tr>
<tr>
<td>June 2010 (GL2010_007)</td>
<td>Deputy Director- General Population Health</td>
<td>Minor revision of GL2010_005, Appendix 2, section 1 Oral/nasogastric oseltamivir, section 1.1 Adults and Children &gt;1 year to align age of children with the Oseltamivir (Tamiflu®) product information (Roche Australia, 4 June 2009)</td>
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ATTACHMENTS
GUIDELINES FOR INFLUENZA IN THE INTENSIVE CARE UNIT – 2010

Most previously healthy adults cease shedding influenza virus in 3-6 days after symptom development, with rapid clinical improvement, and this is shortened by antiviral therapy. Most patients present to hospital between 1-5 days after onset of symptoms and most will still be shedding virus. There is an argument that the more severely ill justify starting antiviral therapy beyond the 48-72 h limit typically used for ‘well’ influenza patients, especially if there is clinical evidence of disease progression related to viral infection. This became practice for treatment of pandemic (H1N1) 2009 influenza (pH1N1) in several intensive care units (ICUs) during 2009.

Data on clinical efficacy of neuraminidase inhibitors (NIs) have almost all been generated on a 5 day 75 mg bd oseltamivir regimen. Increased clearance of drug and potentially reduced gastrointestinal absorption in critically ill patients has prompted empiric use of higher doses, usually 150 mg bd. Similarly, evidence of prolonged viral shedding in the seriously ill has prompted empiric use of 10 day rather than 5 day courses, although there is at present no evidence of increased efficacy. Many studies have shown that oseltamivir treatment reduces mortality in hospitalised patients with seasonal influenza.

Available NIs for use in the ICU may include oral/nasogastric (NG) or intravenous (IV) oseltamivir, inhaled, nebulised or IV zanamivir, and IV peramivir. Not all IV/nebulised formulations of NIs are currently registered for use in Australia. Availability and access to these formulations should be discussed with Infectious Diseases (ID)/Pharmacy. Note: Zanamivir (Relenza®) inhalation powder is only to be administered using the Diskhaler device and should not be reconstituted in any liquid formulation for nebuliser or IV administration.

Failure of a severely ill influenza patient to improve on oseltamivir treatment is not proof of oseltamivir resistance, but this has been reported and may be more common in severely ill and immunosuppressed patients. Approximately 10% of ventilated ICU patients with ongoing pH1N1 infection will have resistant virus detected at 7-10 days although the clinical significance is not always certain. Intravenous peramivir should not be used for treatment of pH1N1 if oseltamivir resistance is confirmed or suspected, due to expected cross-resistance.

The relationship between infectivity and detection of viral RNA by PCR is unknown, but data from hospitalised patients with seasonal influenza suggests that ~25% will still have detectable RNA at one week after treatment and >50% after one week if not treated. Early commencement of treatment shortens the shedding period in severely ill patients but highly immunosuppressed patients may shed virus for very prolonged periods.

ICU patients with influenza-like-illness (ILI) should be tested for influenza using upper and lower respiratory tract sampling. In pH1N1 pneumonia, lower respiratory tract sampling is more sensitive than upper respiratory tract sampling. Influenza antigen

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1. Lancet 2003; 362:1733-
2. editorial comment: J Infect Dis 2009; 200:485-
3. NSW Health Information for prescribers fact sheet 3 May 2010
4. NSW Health Policy Directive PD2010_012, 10 February 2010
5. NSW Health Safety Alert 005/190, 21 October 2009
7. Wang et al; Smith D pers. comm.
8. Inf Ctl Hosp Epidemiol 2007; 28:1071-
9. J Infect Dis 2009; 200:492-
10. NEJM 2009; 361(25):2493
detection using point of care (POC) testing or direct immunofluorescence of nasal/pharyngeal specimens is widely available for rapid screening but is less sensitive than nucleic acid (eg PCR) testing.\textsuperscript{11} If influenza A is detected, subtyping should be performed as soon as possible, and ideally within 72 hours, and interpretation of results discussed with ID/Microbiology (Micro). Influenza-specific serology for ICU patients with suspected influenza infection may also be valuable for a retrospective diagnosis, particularly in patients with negative influenza results from direct testing of respiratory tract specimens.

If NI resistance is suspected in patients failing treatment (eg if immunosuppressed, or contact with known resistant virus, or presentation with influenza-like-illness despite prior NI prophylaxis), resistance testing should be discussed with ID/Micro. This may include: genotypic testing to detect a known mutation (eg the H275Y mutation for resistance to oseltamivir) which can be done on a clinical specimen and is the most rapid test; phenotypic testing for any NI resistance, which is performed on a viral isolate from a clinical specimen; sequencing of the neuraminidase gene. These methods may be used serially or in combination as documented evidence of resistance against oseltamivir, peramivir and zanamivir accumulates.

**Acknowledgements**

These guidelines were prepared with the assistance of A/Professor Jon Iredell (Centre for Infectious Diseases and Microbiology, University of Sydney; Westmead Hospital), Professor Dominic Dwyer (WHO National Influenza Centre, Centre for Infectious Diseases and Microbiology, Institute of Clinical Pathology and Medical Research, Westmead Hospital) and Professor William Rawlinson (South Eastern Area Laboratory Services, Prince of Wales Hospital).
Appendix 1 – Guidance for management of patients with ILI in the ICU

Treatment
1. Adult ICU patients with clinical evidence of ongoing/severe viral illness (fevers, progressive pneumonitis) should be treated with oseltamivir 75-150 mg bd orally or via a NG tube for 5 to 10 days in the first instance. Details of oral oseltamivir dosing regimens for adults and children are shown in Appendix 2. Clear data to guide NG dose and duration are lacking but NG oseltamivir is well absorbed in most ICU patients, and NG dosing should follow oral dosing recommendations.12,13
2. All cases of acute severe community-acquired pneumonia in the setting of an influenza epidemic should be tested for influenza, as given below, and started on presumptive antiviral treatment. Antibiotics should be used in accordance with unit or national guidelines or in consultation with ID/Micro/Respiratory Medicine. Results of investigations may facilitate the decision to cease antiviral agent and/or antibiotics (eg influenza pneumonia without evidence of secondary bacterial infection) or modification of antibiotic cover to target demonstrated infection eg by Staph. aureus.

Laboratory testing
1. All ICU patients with suspected influenza should have nasal (turbinates)/pharyngeal (faucial pillars/tonsils) swabs collected AND lower respiratory tract (BAL, nb-BAL) specimens if possible14, for testing by PCR.
2. All ICU patients with influenza should have subtyping performed as soon as possible.
3. Respiratory tract specimens for resistance testing should be collected (in addition to the initial sample) from ventilated patients between days 7-10 (and again every week if still ventilated and clinical evidence of treatment failure), or in patients failing treatment where NI resistance is suspected. After discussion with Microbiology/Infectious Diseases, these specimens should be referred directly to a laboratory that performs resistance testing with a request for ‘Influenza drug resistance testing’.
4. Influenza serology should be considered for ICU patients with suspected influenza but negative influenza results from direct testing of upper and/or lower respiratory tract specimens. Serum should be collected soon after onset of infection, and again at least 10 days (preferably 21 days) after onset.

Infection Control
1. All ICU patients with syndromes consistent with influenza should be regarded as infectious and precautions applied if they (a) still require antiviral therapy, (b) have a history of illness of less than 14 days and are not on relevant antiviral therapy, and/or (c) are severely immunosuppressed and still hospitalised with influenza.
2. If a single room is unavailable, cohort patients by (a) placing beds at least 2 metres apart, or if not possible (b) use between-bed curtains and space beds at least 1 metre apart.15
3. Consult with ID physician/Infection Control Professional about cessation of precautions, which may be appropriate in recovering immune competent patients after a week (or at least 72 hours) of antiviral therapy.
4. Staff should have current influenza vaccination.
5. All staff, patients and visitors must comply with infection control requirements, including (a) hand hygiene, (b) contact and droplet precautions,(c) respiratory hygiene/cough etiquette.16
6. Staff exposed to aerosol-generating procedures (eg endotracheal intubation, open airway suctioning or opening a ventilator circuit, nebulised medication administration, non-invasive ventilation) must wear a P2 mask, protective eye-wear, disposable impervious gown, and gloves). Vulnerable staff and visitors should not be exposed to aerosol generating procedures.14,17

14 false negative results occur (especially with point-of-care tests in the upper respiratory tract of ventilated cases) and management in the first instance should be based on clinical probabilities
15 MJA 2009; 191 (8): 454-458
16 NSW Health Infection Control Policy PD2007_036
Appendix 2 – Neuraminidase inhibitor dosing guidelines

1 Oral/nasogastric oseltamivir

1.1 Adults and Children >1 year
Oseltamivir (Tamiflu®) product information (Roche Australia, 4 June 2009)

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Adults and Children ≥ 13 years</td>
<td>75 mg twice per day for 5 days</td>
</tr>
<tr>
<td>Children (≥ 12 months up to 13 years)</td>
<td></td>
</tr>
<tr>
<td>≤ 15 kg</td>
<td>30 mg twice daily for 5 days</td>
</tr>
<tr>
<td>&gt;15-23 kg</td>
<td>45 mg twice daily for 5 days</td>
</tr>
<tr>
<td>&gt;23-40 kg</td>
<td>60 mg twice daily for 5 days</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>75 mg twice daily for 5 days</td>
</tr>
</tbody>
</table>

1.2 Children <1 year
The Roche product information for oseltamivir does not recommend use in children under 12 months of age. However, the WHO Clinical management of human infection with pandemic (H1N1) 2009: revised guidance, November 2009 (available at http://www.who.int/csr/resources/publications/swineflu/clinical_management/en/) includes the following recommendations:

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 3 months to &lt;12 months</td>
<td>3 mg/kg/dose twice daily for 5 days</td>
</tr>
<tr>
<td>Children 1 month to 3 months</td>
<td>2.5 mg/kg/dose twice daily for 5 days</td>
</tr>
<tr>
<td>Children 0 to 1 month*</td>
<td>2 mg/kg/dose twice daily for 5 day</td>
</tr>
</tbody>
</table>

* There are no data available regarding the administration of oseltamivir to infants less than one month of age.

1.3 Adults with renal impairment
Oseltamivir (Tamiflu®) product information (Roche Australia, 4 June 2009)

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance &gt;30 mL/min</td>
<td>75 mg twice daily for 5 days</td>
</tr>
<tr>
<td>Creatinine clearance between 10 mL/min and 30 mL/min</td>
<td>75 mg once daily for 5 days</td>
</tr>
</tbody>
</table>

* Treatment is not recommended for patients undergoing routine haemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease; and not for patients with creatinine clearance ≤10 mL/min.

2 Zanamivir inhalation
Refer to product information, and Use of oseltamivir (Tamiflu®) and zanamvir (Relenza®) for treatment of influenza – information for prescribers available at http://www.emergency.health.nsw.gov.au/swineflu/professionals/criticalcare.asp

3 Other formulations and NIs
If required, other formulations and NIs which are not currently registered for use in Australia may be available through special access arrangements. Consult Infectious Diseases/Pharmacy departments regarding availability and access to eg IV peramivir, nebulised or IV zanamivir, IV oseltamivir.