



Critical care management of adults with influenza with particular reference to H1N1 (2009)

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Introduction

This updated adult practice note is based on guidance and published literature collated and reviewed by the Health Protection Agency (HPA), the Royal College of Anaesthetists, the Intensive Care Society, the Faculty of Intensive Care Medicine and the Intensive Care National Audit and Research Centre. This guidance may change, so please check the web site regularly as more information becomes available.

Riquelme *et al* highlight in their Spanish & Chilean cohort differences in the affected groups and outcomes from H1N1 (2009) when compared to seasonal influenza; younger age, less co-morbidity, more extensive radiographic extension and more severe respiratory compromise and intensive care unit admission. ERJ Express, Nov 2010.

It should be noted that, at the time of writing, there is a substantial co-circulation of influenza B virus within the Greater London area (HPA data). Management of these cases should be similar to the pandemic influenza A(H1N1) 2009; please make sure that your local laboratory testing algorithm includes flu B.



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Infection control

	Entry to cohorted area but no contact with patients	Close patient contact (within one metre)	Aerosol-generating procedures
Hand hygiene	✓	✓	✓
Gloves	✗ ^b	✓ ^c	✓
Plastic apron	✗ ^b	✓	✗
Gown	✗	✗ ^{d,e}	✓ ^e
Surgical mask	✓ ^f	✓	✗
FFP 3 respirator	✗	✗	✓
Eye protection	✗	Risk assesement	✓

Note that the infection control guidance from 2009 is still appropriate for 2010/2011.

It can be found at: www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_110899.pdf

Footnotes:

Standard Infection control principles apply at all times

- Where possible, procedures that might generate an infectious aerosol, Aerosol Generating Procedures (AGPs), should be performed in closed, single-patient areas with minimal staff present. **Potential AGPs include intubation and ventilation, HFOV, open tracheal suction, tracheostomy care, bronchoscopy, CPR, NIV, induction of sputum.** After a review of the evidence, nebulisers have been removed from the World Health Organization’s list of potential AGPs.
- Gloves and an apron should be worn during certain cleaning procedures.
- Gloves should be worn in accordance with standard infection control principles. If glove supplies become limited or come under pressure, this recommendation may need to be relaxed. Glove use should be prioritised for contact with blood and body fluids, invasive procedures and contact with sterile sites.
- Consider a gown in place of an apron if extensive soiling of clothing or contact of skin with blood or other body fluids is anticipated (e.g. during intubation or when caring for infants).
- If non-fluid repellent gowns are used, a plastic apron should be worn underneath.
- For pragmatic reasons, surgical masks (fluid repellent) are recommended for use at all times in cohorted areas. If mask supplies become limited or come under pressure, then their use should be limited to close contact with a symptomatic patient (within one metre).

- Outbreaks of H1N1 influenza have occurred in the hospital setting and viral transmission to healthcare workers has occurred in the UK, mainly from patients who have presented atypically.
- The Joint Committee on Vaccination and Immunisation (JCVI) includes front line healthcare workers as a key group to be offered seasonal flu vaccine www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_121931.pdf.
- Appropriate personal protective equipment (PPE) should be used while caring for patients with suspected or confirmed influenza until the patient is deemed no longer infectious; which is usually once they have completed a course of anti-virals and are no longer symptomatic; this may be longer in the immunocompromised and sequential testing may be advisable – liaise with local microbiologist.
- When performing potentially infectious aerosol generating procedures, single use protective gloves, gown, eye protection and an FFP3 mask should be used
- Staff requiring FFP3 level mask protection must undergo fit-testing. Each time they wear a FFP3 mask they should perform a fit check. See the Appendix on how to perform a fit check.
- Hand hygiene plays an important role in the decrease of transmission.
- Viral and bacterial filters should be used on equipment where appropriate.
- There is currently no evidence to suggest that the virus strains that cause severe/fatal disease differ from those causing mild influenza-like illness. It seems likely that host factors may be more important in determining the severity of illness.
- Staff should remember that the hospital environment is not the only risk factor for exposure and infection. If widespread community transmission is occurring, staff will continue to be at risk while not at work.

Patient presentation (based on 2009 data)

- Most hospitalised patients have a history of flu-like illness consisting of a combination of pyrexia, cough, breathlessness, headache, sore throat and nausea or vomiting, but this may be mild. Some may deteriorate rapidly or present *in extremis*. Although most have respiratory symptoms, some have signs of dysfunction in other systems and rarely patients have presented with abdominal or CNS symptoms only.
- Fever may be absent at presentation in up to 30% of patients.
- The 2009 hospitalisation rate in the UK was an estimated 1.3 - 2.5%. Case series demonstrate that a high proportion (10-30%) of laboratory confirmed, hospitalised patients required critical care in 2009.
- Although up to 50% of adults hospitalised in 2009 were previously healthy, risk factors identified for the development of complicated illness include: asthma and COPD; morbid obesity; pregnancy and the immediate post-partum period; chronic cardiovascular, pulmonary, renal, hepatic, or neurological conditions; diabetes mellitus & immunosuppression.
- Obesity, chronic respiratory disease, radiologically-confirmed pneumonia and a C-reactive protein >100mg/l increase the likelihood of admission to critical care or death in hospital.
- The principle clinical syndrome leading to hospitalisation and critical care is diffuse viral pneumonia, often associated with rapidly progressive acute respiratory failure and ARDS (approximately 50-75% of intensive care admissions).

- Radiographic findings commonly include diffuse mixed interstitial and alveolar infiltrates and most have bilateral changes, although focal, lobar distributions may be seen and raise the possibility of superimposed bacterial infection.
- In the SwiFT data, 421 of 547 confirmed H1N1 cases referred to ICUs (77%, 95% confidence interval 73% to 80%) were reported to have received advanced respiratory support (as defined in the Critical Care Minimum Data Set) at any time during critical care.

Clinical management

Respiratory

- Rapidly progressive respiratory failure is relatively common preceding ICU admission, therefore ward-based monitoring must include respiratory rate and SpO₂ on a regular basis.
- An 'early warning system' of clinical patient observation and prompt referral to critical care and/or outreach teams may help identify and manage deteriorating patients.
- Intubation versus non-invasive ventilation:
 - Non-invasive ventilation (NIV) has been used with success in patients with:
 - Mild to moderate pneumonitis
 - Chronic co-morbidities that have precluded intubation

Patients with severe, deteriorating respiratory failure do not benefit from NIV and prompt intubation is advocated for these patients.

- Ventilatory strategies
 - Profound refractory hypoxaemia is relatively common and may persist for 48–72 hours on antiviral therapy before improving.
 - In SwiFT the median duration of advanced respiratory support among those that received it was 9 days, with an interquartile range of 4 to 17 days. Overall (including those that received no advanced respiratory support), the mean duration was 10 days (standard deviation 13 days).
- Pulmonary compliance should be assessed in all ventilated patients
 - Compliance may be **normal**
 - This group of patients require relatively modest inflation pressures to achieve Vt of 6-8 ml/kg
 - Use of high airway pressures, PEEP or high frequency oscillation (HFO) in these patients may lead to alveolar over-distension or worsen oxygenation and haemodynamics.
 - Compliance may be **decreased**
 - This group of patients may benefit from higher levels of PEEP, airway pressure-release ventilation (APRV) or HFO.
- Prone positioning and nitric oxide have also been used successfully for treating refractory hypoxaemia.
- HFO has been used successfully for treating refractory hypoxaemia but virus-filtered circuits and appropriate personal protective equipment should be used.

- Extra-corporeal membrane oxygenation (ECMO) has been used successfully for treating refractory hypoxaemia in selected patients.

The current referral criteria for ECMO are found at:

www.uhl-tr.nhs.uk/ourservices/medical-services/f--h-medical-services/heart-services/extra-corporeal-membrane-oxygenation-

- All referrals for ECMO should be directed to the University of Leicester Hospital NHS Trust, by calling 0116 287 1471 and asking for the ECMO co-ordinator.
- In conclusion, efforts should be made to adopt an advanced mechanical ventilation strategy including protective lung ventilation, a significant negative fluid balance using diuretics or RRT, prone positioning, APRV / HFOV, nitric oxide followed by early referral for ECMO (i.e. within 7 days) as this is what the CESAR trial highlighted.

Cardiovascular

- Moderate hypotension is relatively common with predictable increases in cardiac output and decreases in systemic vascular resistance.
- Most patients respond to fluid therapy +/- vasopressor therapy.
- However, volume expansion should be undertaken with caution as over-hydration seems to worsen oxygenation and outcome.
- Patients should only receive fluid if they are “fluid responsive”.

Renal

- 112 of 547 confirmed H1N1 cases (20%, 95% confidence interval 17% to 24%) were reported to have received renal support (as defined in the Critical Care Minimum Data Set) at any time during critical care. Swift data.
- Negative fluid balance by either diuresis or RRT improves oxygenation in many cases.

Microbiological – look for updates on the HPA website regarding sampling regimens

www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1191942171468

- If influenza is suspected then commence antiviral therapy and arrange appropriate sampling **before** results are available.
- Before a patient’s influenza status is known they should be nursed in isolation where possible.
- Confirmed influenza cases can be nursed in open, cohorted areas if side rooms are unavailable.
- Patients should have viral swab samples taken from the upper respiratory tract e.g. combined nose and throat swabs or nasopharyngeal samples at presentation.
- Staff should wear PPE for taking samples.
- Upper respiratory tract specimens may be false-negative in patients with evidence of lower respiratory tract involvement; ET aspirates, BAL or NDBL samples should be obtained in these patients, in addition to upper respiratory tract samples. Appropriate diagnostic sampling should be repeated, and anti-

viral therapy continued when initial tests are negative but clinical suspicion remains high. Liaise with virology if unsure; some rapid tests have a low sensitivity.

- Infection control measures can be discontinued once the patient is symptom free – the exception would be patients who are thought to be at risk of prolonged excretion of the virus or developing oseltamivir resistance such as immunocompromised individuals, or those who are known to have an oseltamivir-resistant strain. If possible, in these situations sequential testing should be undertaken and infection control measures applied until influenza is not evident upon sequential testing. This will require close liaison with infection control and virology.
- Antiviral susceptibility testing should be considered in ITU patients with confirmed H1N1 and in all who fail to improve after 5 days of therapy, or earlier if antiviral resistance is likely according to epidemiological and virological data.
- Shedding of confirmed resistant virus should be monitored sequentially; repeat testing 5 days following start of treatment and periodically thereafter until at least two sequential tests are negative. Unlike the summer of 2009, the current testing capacity to assess presence of virus in respiratory samples are substantial and robust in specialist virology centres and university hospital virology laboratories. Access to PCR tests could be limited or delayed in district general hospital microbiology laboratories; hence intensivists should liaise with DGH consultant microbiologists for a suitable arrangement.
- Routine protocols for the investigation of conventional pneumonias should be followed.
- Antibiotic use should follow local and national guidelines; guidance should be sought from local infection specialists.
- Antiviral treatment within 48 hours of illness onset is protective against development of concurrent bacterial infections [HPA study]. Antiviral treatment should be given to hospitalised patients even if they present with an illness onset of longer than 48 hours.
- Concurrent bacterial infections are associated with admission to ICU when the bacterial infection develops before the date of admission to hospital. Concurrent bacterial infection has been reported in international clinical series (20-25%). The prevalence of concurrent bacterial infection in lab-confirmed 2009 H1N1 cases in England was low (76/20,335, 0.9%) during the pandemic, but initial reports from clinicians suggest that rates of bacterial infection may be higher this season (2010/11).
- *Streptococcus pneumoniae*, group A *Streptococcus*, *Staphylococcus aureus* and Gram negative rods have been isolated.
- Isolated cases of MRSA & PVL-expressing staphylococcal infections have been described and clinicians should be alert to this possibility.

Anti-viral drug therapy – look at the DH and HPA websites for updates

www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1191942171468

- Unless epidemiological or laboratory data suggest drug resistance is likely, oseltamivir remains the first line antiviral agent for H1N1 (2009) infection, including the treatment of infected pregnant women.
- Early treatment is associated with optimal outcomes and is recommended, but improvements may still be seen when treatment is commenced beyond the first 48 hours of illness.
- Studies show that oseltamivir is well absorbed enterically in critically ill patients.

- A 75 mg dose twice daily achieves plasma levels comparable to those in patients with uncomplicated illness and adequate concentrations are achieved to maximally inhibit viral neuraminidase, including the treatment of infection in obese patients.
- The conventional oseltamivir dose for uncomplicated illness is 75mg bd for 5 days. 150mg bd for 10 days is recommended in critically ill patients in an attempt to limit the duration of viral shedding, prevent reported viral rebound and to optimise drug levels in the lungs. This is an unlicensed dosage but there have not been any reported safety issues to date.
- Oseltamivir schedules exist for those with stable impaired renal function. Liaise with your pharmacist & renal team.
- Intravenous zanamivir remains unlicensed but is available for compassionate use following discussion with the manufacturer.
- Inhaled zanamivir is not recommended in critically ill patients as it is not systemically active. Ventilator circuits have become blocked when the inhaled preparation has been used to make nebuliser solution and this should be avoided.
- Rarely patients can be infected with oseltamivir-resistant strains, or resistance can arise during treatment. This is most likely to occur in immunocompromised individuals as was the case with a small cluster of haematological, immunocompromised patients in 2009.
- Oseltamivir resistance is uncommon in H1N1 (2009) infection and zanamivir resistance remains rare. However, severely immunocompromised individuals, e.g. haem oncology patients, are a notable risk group for the emergence of oseltamivir resistance and prolonged viral shedding and in these instances zanamivir may be considered for first line therapy. This is likely to be a local decision guided by virological and epidemiological information. Please refer to the HPA web site for updated information. There is no evidence to support the use of combination neuraminidase therapy.
- Intravenous zanamivir may be considered on a compassionate use basis when oseltamivir resistance is known or suspected or if there is concern about the absorption of the NG oseltamivir in the critically ill patient.

Planning and triage

Guidance on surge planning and critical care triage can be found in the *Report of the Swine Flu Critical Care Clinical Group and Key Learning Points for Future Surge Planning* (1 July 2010). Department of Health gateway reference 14425; www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117129

Other

Sedation requirements were unexpectedly high in some patients in 2009. These reports were from outside the UK, where neuromuscular blockage was sometimes required.

Steroids

- There is no evidence to support the use of high dose methylprednisolone or hydrocortisone in the treatment of severe pH1N1 infection and their use should be restricted to controlled clinical trials.
- In H5N1 (avian flu) they may worsen outcome and increase viral shedding times.
- Intensivists should restrict replacement steroid therapy to those with evidence of adrenal suppression.

Extra-pulmonary complications

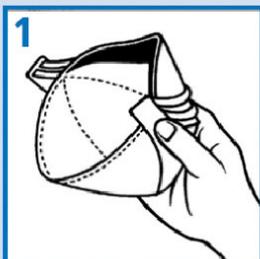
- Raised CK is a frequent finding and cases of myositis and rhabdomyolysis have been reported.
- Myocarditis and pericarditis are relatively uncommon on ECG, but have been reported at post mortem.
- RV dilatation and systolic dysfunction on echocardiography has been reported in up to 50% of critically ill patients and moderate or severe abnormalities in approximately 25%.
- Neurological complications are less common in adults than in children, but encephalopathy and encephalitis have been reported.
- Post-mortem evidence may provide clarity to the underlying cause of death and pathogenesis.
- Increased rates of pulmonary embolism in critically ill patients have been reported in radiological and post-mortem series. DVT prophylaxis is routine in ICU.

Appendix 1

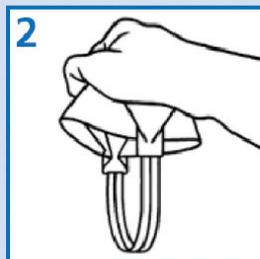
HOW TO FIT AND FIT CHECK AN FFP3 RESPIRATOR

FOLLOW THESE FIVE STEPS TO FIT YOUR RESPIRATOR CORRECTLY

Tip: It may be helpful to look in the mirror when fitting your respirator



Hold the respirator in one hand and separate the edges to fully open it with the other hand. Bend the nose wire (where present) at the top of the respirator to form a gentle curve.



Turn the respirator upside down to expose the two headbands, and then separate them using your index finger and thumb. Hold the headbands with your index finger and thumb and cup the respirator under your chin.



Position the upper headband on the crown of your head, above the ears, not over them. Position the lower strap at the back of your head below your ears.



Ensure that the respirator is flat against your cheeks.



Mould the nosepiece across the bridge of your nose by firmly pressing down with your fingers until you have a good facial fit. If a good fit cannot be achieved, try another size or design of FFP3.

Suggested reading

Clinical reviews

- Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM, Zaki SR, Hayden FG, Hui DS, Kettner JD, Kumar A, Lim M, Shindo N, Penn C, Nicholson KG. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med*. 2010 May 6;362(18):1708-19
- Clinical management of pandemic 2009 influenza A(H1N1) infection. Hui DS, Lee N, Chan PK. *Chest*. 2010 Apr;137(4):916-25. Epub 2009 Dec 18
- Practical lessons from the first outbreaks: clinical presentation, obstacles, and management strategies for severe pandemic (pH1N1) 2009 influenza pneumonitis. Funk DJ, Siddiqui F, Wiebe K *et al*. *Crit Care Med*. 2010 Apr;38(4 Suppl):e30-7

Epidemiology and Clinical Series

- Rowan KM, Harrison DA, Walsh TS, McAuley DF, Perkins GD, Taylor BL, *et al*. The Swine Flu Triage (SwiFT) study: Development and ongoing refinement of a triage tool to provide regular information to guide immediate policy and practice for the use of critical care services during the H1N1 swine influenza pandemic. *Health Technol Assess*, in press.
- Evidence of Person-to-Person Transmission of Oseltamivir-Resistant Pandemic Influenza A(H1N1) 2009 Virus in a Hematology Unit. Moore *et al*. *JID* 2011;203 (1 January)
- Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May-September 2009). Nguyen-Van-Tam JS, Openshaw PJ, Hashim A, Gadd EM, Lim WS, Semple MG, Read RC, Taylor BL, Brett SJ, McMenamin J, Enstone JE, Armstrong C, Nicholson KG; Influenza Clinical Information Network (FLU-CIN). *Thorax*. 2010 Jul;65(7):645-51
- Pandemic Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Pebody RG, McLean E, Zhao H *et al*. *Euro Surveill*. 2010 May 20;15(20). pii: 19571
- *N Engl J Med*. 2009 Nov 12;361(20):1935-44. Epub 2009 Oct 8. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. Jain S, Kamimoto L, Bramley AM *et al*. *N Engl J Med*. 2009 Nov 12;361(20):1935-44. Epub 2009 Oct 8
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- Critically ill patients with 2009 influenza A(H1N1) infection in Canada. Kumar A, Zarychanski R, Pinto R *et al*. *JAMA*. 2009 Nov 4;302(17):1872-9. Epub 2009 Oct 12
- Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. Zarychanski R, Stuart TL, Kumar A *et al*. *CMAJ*. 2010 Feb 23;182(3):257-64. Epub 2010 Jan 21
- Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009. *n engl j med* 361;20 nejm.org november 12, 2009

- Critical illness with AH1N1v influenza in pregnancy: a comparison of two population-based cohorts. Knight M, Pierce M, Seppelt I *et al.* BJOG. 2010 Oct 13. doi: 10.1111/j.1471-0528.2010.02736.x
- Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Kumar D, Michaels MG, Morris MI *et al.* Lancet Infect Dis. 2010 Aug;10(8):521-6. Epub 2010 Jul 9
- Novel H1N1 Influenza In Hematopoietic Stem Cell Transplant Recipients: Two Center's Experience. Taplitz R, Espinosa-Aguilar L, Green J *et al.* Biol Blood Marrow Transplant. 2010 Aug 10. [Epub ahead of print]

Guidelines and Reports

- WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses (Feb 2010). Available at www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html (last accessed 30 Nov 2010)
- Pandemic H1N1 2009 influenza: clinical management guidelines for adults and children. Department of Health, 30 Oct 2009. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107769 (last accessed 30 Nov 2010)
- Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave. Health Protection Agency, v4 2 December 2009 www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1258560552857 (last accessed 30 Nov 2010)
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Critical Care Strategies

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- Use of extracorporeal life support to support patients with acute respiratory distress syndrome due to H1N1/2009 influenza and other respiratory infections. Wong I, Vuylsteke A. Perfusion. 2010 Sep 8. [Epub ahead of print]
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- Neuromuscular blockers in early acute respiratory distress syndrome. ACURASYS Study Investigators, Papazian L, Forel JM, Gacouin A *et al.* N Engl J Med. 2010 Sep 16;363(12):1107-16

Extra-pulmonary Complications

- Complications of seasonal and pandemic influenza. Rothberg MB, Haessler SD. Crit Care Med. 2010 Apr;38(4 Suppl):e91-7
- Acute kidney injury and 2009 H1N1 influenza-related critical illness. Bellomo R, Pettilä V, Webb SA *et al.* Contrib Nephrol. 2010;165:310-4. Epub 2010 Apr 20
- Neurologic and muscular complications of the 2009 influenza A (H1N1) pandemic. Davis LE. Curr Neurol Neurosci Rep. 2010 Nov;10(6):476-83
- Right and left heart failure in severe H1N1 influenza A infection. Brown SM, Pittman J, Miller RR *et al.* Eur Respir J. 2010 Jun 1. [Epub ahead of print]