



Paediatric practice note for the management of critically ill children with pandemic (H1N1) 2009 Influenza

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Caveat

This practice note is presented to clinical colleagues to assist the management of critically ill children with H1N1 (2009) influenza. The recommendations are based primarily on paediatric ICU practice and arise from the international H1N1 ICU network teleconferences held since June 2009, with the most recent occurring on 6th January 2011 and recent publications and guidance.

The participants have included intensivists and paediatricians from Scottish, English, Northern Irish and Welsh hospitals, along with colleagues from Mexico, the US, Canada, Australia, New Zealand and the Republic of Ireland, as well as representatives from the Department of Health and the World Health Organisation. The views presented reflect the consensus of those participating and who have had direct experience of ICU treatment of H1N1 patients in the current pandemic. Although verified as far as possible, the opinions are clearly those of the individuals. The HPA considered it useful to facilitate these telephone conferences with the Royal College of Paediatrics and Child Health, the Royal College of Anaesthetists, the Paediatric Intensive Care Society, the Intensive Care Society, BPAIIG, and APAGBI. They welcomed the opportunity to share some of the outcomes.

The evidence base for this document is predominantly expert opinion; otherwise it has been referenced. It is not a systematic review. Clinicians are encouraged to collaborate with ethically approved research studies (for example ICNARC, SWIFT and MOSAIC) and NIGB authorised clinical information networks (for example PICANET) so we can continue to increase our knowledge of this disease. The RCPCH Clinical Standards Committee has reviewed the document and it is considered safe and fit for practice; however the document has not undergone the formal College endorsement process for documents relating to clinical standards due to the urgent need for rapid processing.

Presentation

Throughout the pandemic the age-specific hospitalisation ratios (i.e. the number in hospital per head of population of that same age) were consistently high for the under 5s. Although, hard hospital data is not available at the current time, the consensus is that during the current influenza activity this is not as marked, particularly with respect to high dependency or critical care (levels 2 and 3). In addition the demographics of children admitted to critical care will be affected by co-circulating winter pathogens such as respiratory syncytial virus (RSV). RSV is currently circulating in significant amounts but is likely to decrease over the forthcoming weeks. The use of vaccination and the exposure of many children to H1N1 (2009) last year as demonstrated by serological surveys carried out by the HPA during the latter part of 2009 is also likely to have affected the number of susceptible children and therefore the numbers admitted to critical care units.

- Symptoms of influenza are similar to other treatable diseases in children therefore clinicians should be mindful of a differential diagnosis.
- In a UK published cohort (n=13), critical illness in the paediatric population with H1N1 (2009) influenza appears mostly to affect children over five years of age with co-morbidities (median age nine years versus 2.7 years in the historical influenza cohort versus 5.7 years in a contemporary hospitalised cohort).¹ However, recent UK data shows that children under the age of five years without co-morbidities are also at risk of severe disease. In the 36 deaths reported to the Centres for Disease Control and Prevention USA (CDC) the median age was also nine years but the range was broader (two months to 17 years) and seven affected were under five years including five under two years.²
- Most, but not all, severely ill children with H1N1 (2009) during the pandemic had comorbidities. Severe neuro-developmental problems (often associated with chronic respiratory diagnoses) and immunodeficiency are noted.^{1 3}
- Risk factors associated with severe disease caused by H1N1 (2009) have been identified in adults and children. However, ~80% of children under 5 years old admitted with H1N1 (2009) influenza had no risk factors.⁴
- The predominant presentation of H1N1 (2009) in children is as a respiratory illness with cough, tachypnea, dyspnoea and desaturation. Fever, though not universal in the hospitalised population, occurred in all those admitted to critical care studied during the pandemic.^{1 3}
- Shock has been a feature of critically ill children presenting with H1N1 (2009) influenza to a greater degree than usually seen in seasonal influenza cohorts.^{1 4}
- Severe gastrointestinal disease (nausea, vomiting, diarrhoea, abdominal pain) is a recognised presentation of H1N1 (2009) influenza.
- Amongst paediatric cases infected with the H1N1 (2009) virus, while infrequent, new neurological disease (encephalitis with coma or status epilepticus) can be a feature of the presentation and may be the sole symptom.⁵
- H1N1 (2009) influenza may cause some children with chronic sub-clinical disease to present, for example with diabetic keto-acidosis.¹
- Laboratory confirmed secondary infection was seen in 10 of a series of 23 paediatric deaths in the US who had microbiology results available.²
- All patients admitted to hospital with influenza-like illness should be considered for treatment with empiric broad-spectrum antibiotics and antiviral therapy. Antibiotics therapy should be given to all patients with a critical illness. This is particularly important given emerging evidence of an increase in the number of bacterial co-infections or secondary infections associated with confirmed cases of influenza since mid December 2010. Consideration and exclusion of other pathologies (e.g. invasive group A streptococcal infections (iGAS), meningococcal sepsis, herpes encephalitis) must be part of the assessment of critically ill children at this time.

Consideration for escalation/referral to critical care facilities may include:

- Hypoxaemia ($\text{SpO}_2 < 94\%$) resistant to high flow oxygen therapy.
- Worsening respiratory distress characterised by: severe, recurrent, prolonged apnoea requiring resuscitation; worsening tachypnea with gasping or grunting; or a rising pCO_2 on sequential blood gas analysis.
- Cardiovascular collapse/shock (inadequate tissue perfusion) that does not respond to a fluid resuscitation (equal to or greater than a total of 20 ml/kg of 0.9% sodium chloride or Hartmann's).
- Encephalitis with coma (GCS < 9) or seizures requiring intubation for airway control.

Respiratory disease

- Hypoxaemia is a common cause for escalation to critical care, so saturation monitoring on the ward is an important observation, along with clinical signs of respiratory distress and exhaustion.
- Critical care outreach and early warning scoring systems may be helpful in identifying patients who should be considered for escalation.
- Respiratory illness in influenza may range from a bronchiolitic like picture through lobar pneumonia to acute respiratory distress syndrome (ARDS). In the cohorts of children ventilated for respiratory disease the predominant picture was of ARDS, with four quadrant infiltrates on X-ray and poor lung compliance. Severe hypoxaemia has also been described with relatively normal lung compliance in some critically ill adults and children. Experience in the adult group supports early intubation and ventilation. Experience in children is limited.
- Non-invasive ventilation (NIV) has been used but appears to confer no advantage in the ARDS group. Use of NIV requires particular infection control measures.
- Children will present during the 2010/11 influenza season with a bronchiolitic picture and type 2 respiratory failure (CO_2 retention and hypoxaemia) and this may be due to H1N1 (2009) influenza, RSV or other respiratory viruses. NIV may be of use, particularly in the cases where severe hypoxaemia is not the predominant symptom. NIV has had a role in weaning and step-down care in the adult critically ill H1N1 (2009) population. NIV can also be considered in the convalescent phase.
- Extra corporeal membrane oxygenation (ECMO) has been used and ECMO clinicians would encourage early discussion of potential cases. Referral should be made before seven days of high oxygen ($\text{FiO}_2 > 0.8$) or high pressure ($\text{PIP} > 30\text{cmH}_2\text{O}$) ventilation. Multi-organ failure does not preclude ECMO therapy, see appendix 1 for ECMO referral guidelines.
- Embolic phenomena (deep vein thrombosis and pulmonary embolism) have been described as a complicating factor in adult cases. The impact of this on paediatric practice is currently unknown.
- Following the resuscitation phase, fluid restriction and diuresis are indicated as in ARDS, but not the use of high dose steroids.

Cardiovascular disease and shock

- Shock is recognised at presentation (8/13 in the UK series reported during the pandemic) and tends to be a septic picture of high output and low systemic vascular resistance. This is in contrast to seasonal flu experience, where shock is unusual.
- Aggressive fluid resuscitation and early use of inotropes in a targeted fashion (urine output, SvO₂, lactate) is appropriate.
- In general corticosteroids should not be used in critically ill patients with H1N1 2009 influenza.
- High dose steroids are associated with increased mortality in sepsis.^{6 7 8 9}
- In a recent adult randomised controlled trial, low (replacement) dose corticosteroids were not associated with an increase in survival or reversal of shock but were associated with an increase in secondary infection, including new sepsis and septic shock.¹⁰
- The use of low dose replacement corticosteroids in critically ill children without catecholamine resistant shock should only be considered in the context of a clinical trial.¹¹
- Catecholamine resistant shock occurred in four of the eight paediatric UK cases studied during the 2009/10 pandemic. Vasopressors and replacement dose steroids have been used in this context.
- Multi-organ failure is not a contraindication to ECMO (see above).
- Myocarditis has been described in children with influenza. This has been associated with a marked tachycardia. The prognosis is unclear, though influenza-related myocarditis usually has a good prognosis for recovery. Cardiac enzymes can be raised (troponin and CK-MB) and this must be differentiated from the raised CK due to myositis or rhabdomyolysis that may also be seen in influenza.
- Early echocardiography in shocked children is recommended to exclude myocarditis as a cause of circulatory failure.

Neurological disease

- Seizures and status epilepticus and encephalopathy with altered consciousness have been seen as the presenting feature of H1N1 2009 influenza in children.^{5 12}
- Seizure control and airway management should follow standard guidelines.
- CT scans should be considered as per usual practice to exclude other pathology. This has revealed other pathology in some cases of H1N1 (2009) influenza (for example cerebral oedema and infarction).⁵
- Lumbar puncture has a role in excluding other causes of meningoencephalitis (for instance herpes simplex virus types I & II).
- The empirical use of aciclovir should be considered for all infants with a neurological presentation pending a HSV PCR result on CSF.
- Non-specific EEG abnormalities have been described.
- The prognosis in isolated neurological presentation where described outside the critical care setting appears good.⁴ Acute neurological symptoms should not limit other therapy, except where clear evidence of an irreversible deficit exists.
- Aspirin in association with influenza is associated with Reye's syndrome. Both diclofenac and mefenamic acid are associated with a worse prognosis in influenza related encephalopathy.¹¹

Renal replacement therapy

- Renal replacement therapy has been required by critically ill adults and children with H1N1 (2009) infection. Paediatric experience is limited.

Microbiology and Infection control

- Local guidelines for infection control should be followed.
- It is appropriate to observe full infection control measures for all suspected cases pending laboratory results. If isolation is feasible, that is preferred to cohorting. Strict hand hygiene between patients must be maintained.
- Immunofluorescence is not sufficiently sensitive for detection and so PCR should be used.
- Virus detection by PCR from the upper and lower respiratory tract can vary during the course of the illness. In intubated children it is preferable to also send endotracheal aspirates (ETA) or non-directed bronchoalveolar lavage (NDBL) for analysis. Note that samples from nose and throat may be negative when lower tract secretions are still positive.
- Full personal protective equipment is required during potential infectious aerosol generating procedures (AGPs) such as suctioning, intubation and bronchoscopy. Refer to current DH and HPA infection control guidelines regarding list of potential infectious AGPs.¹²
- NIV is potentially an infectious aerosol generating procedure and full PPE should be worn when caring for patients with confirmed or suspected influenza. Nosocomial spread has been reported in this context associated with sub-optimal PPE usage.
- Several cases of H1N1 (2009) influenza have required high frequency oscillatory ventilation (HFOV). This may cause environmental contamination when oscillators are used without exhaust scavenging or filters.
- Serial sampling of confirmed cases may be considered in discussion with the local laboratory. Repeat testing in the context of on-going/worsening clinical picture may have a utility with regard to the early detection of detection of oseltamivir resistance, guiding duration of prolonged treatment with oseltamivir, or consideration of alternative antivirals.
- On admission and or when deterioration occurs, viral and bacterial investigations on lower respiratory tract samples, including culture and sensitivity where possible, should be repeated to screen for other pathogens (endemic seasonal viruses, which may co-infect, and bacterial super-infection).
- In children with on-going respiratory symptoms infection control should be maintained.

Antimicrobial therapy

- Concurrent bacterial infection has been reported with *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*. In particular, the number of cases of iGAS has increased in recent weeks and now exceeds the number usually seen at this time of year
- Empirical treatment with broad-spectrum antibiotics that will cover the above pathogens, according to local policy (or national guidance where issued), is appropriate in the setting of severe H1N1 (2009) influenza causing respiratory or multi-organ failure.
- Treatment with oseltamivir should be started on clinical grounds while awaiting test results.
- Oseltamivir dosing should follow current national guidelines.

- Liaise with local experts for most up-to-date antiviral guidance.
- Some clinicians have doubled the dose in older critically ill children; however the risks and benefits of this are unclear.
- Oseltamivir dose should not be doubled in children under the age of one year.
- Concerns have been raised about enteral absorption of oseltamivir. This has NOT been a common problem in the critically ill population to date; many patients will have adequate systematic levels of oseltamivir when the capsules are dissolved and delivered through a naso-gastric tube.
- Under compassionate use an intravenous preparation of zanamivir has been used in cases of suspected poor enteral absorption where inhaled Zanamivir could not be used.¹³ No significant data is available for children.¹³ Experience in the use of intravenous zanamivir is limited; however, experts may consider using intravenous zanamivir in certain circumstances and with reference to HPA guidance;

Triage of children in-to and out-of critical care.

Triage should only be considered when demand exceeds capacity and all options for transfer of care have been exhausted. To date there has been no need for triage.

- Local ICU triage policies should emphasise the need for peer review of triage decisions, discussions with family members, transparency of the decision process and proper documentation of decisions. Decision making processes should be open and accountable.
- There are models such as the Ontario Triage Protocol, which are accepted by some as being an acceptable and ethically sound framework to assist in making clinically based triage decisions where demand exceeds capacity and where the focus is on outcomes across the whole system.¹⁴ However at present there is no useful paediatric critical care triage-scoring tool to use with the Ontario Protocol.
- In the event that a validated triage-scoring tool is developed for triage in or out of PICU, it should only form part of a properly constituted ethical triage framework as outlined above.
- Mathematical models can be used in building a picture of the importance of both anticipated length of stay and eventual outcome when making triage decisions. Such analysis of UK paediatric data indicates that pre-existing co-morbidities, particularly if multiple, are associated with worse outcome and longer stay. At this early stage of triage development, it is difficult to be certain of the extent to which these differences will have clinical relevance or ethical acceptance or operational value.

The Paediatric Intensive care society has published additional information regarding triage in the paediatric community following the Joint Briefing from the Intensive Care Society, the Paediatric Intensive care society and Association of Paediatric Anaesthetists in June 2009.¹⁵

Appendix 1

H1N1 Paediatric ECMO Referral Guidelines

Patients from 1 month of age to 18 years

- Severe but potentially reversible respiratory failure, suspected or confirmed H1N1
- PaO₂:FIO₂ ratio <10 kPa or pH ≤ 7.2
- No Contraindication to limited heparinisation (i.e. intracranial bleeding)
- ≤ 7-9 days high pressure (>30cmH₂O) or high FIO₂ (0.8) ventilation, depending on age.

Please note that multi-organ failure is not a contraindication but a moribund condition is.

To refer please call your nearest ECMO centre

Scotland:	Yorkhill on 0141 201 0255 (Neonatal Surgery)
Newcastle:	Freeman 0191 223 1016 (identify as an ECMO referral)
Leicester:	Glenfield on 0300 303 1573 (ask for the ECMO Coordinator)
London:	GOSH on 0207 829 8652 (identify as an ECMO referral)

If your local unit is full the coordination of cases to other centres will be carried out by the ECMO unit. ECMO units are always happy to discuss cases if you are not sure, or would like to talk about conventional treatment.

Transport

The ECMO team will transport your patient for you. Please note that almost all patients can be transported successfully, however sick they are, transport may involve the use of mobile ECMO

Appendix 1 kindly provided by Dr Giles Peek, on behalf of Glenfield Hospital ECMO Centre, University Hospitals of Leicester NHS, 13th November 2009.

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