

# 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 paediatric cases of pandemic (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 23 September 2009.

These 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, BPAIG, 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 & Flu-CIN) so we can continue to increase our knowledge of this disease. The RCPCH Quality of Practice 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.

## Presentation

Numbers of children admitted to critical care units are small at this time. Consequently data is limited at present and may not be generalisable. Demographics of children admitted to critical care are likely to change greatly as the anticipated second wave starts and disease is complicated by co-circulating winter pathogens such as human respiratory syncytial virus (hRSV). The introduction of vaccination is also likely to change the demographics of children admitted to critical care units.

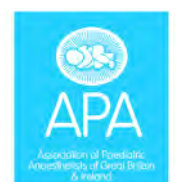
1. Symptoms of influenza are similar to other treatable diseases in children therefore clinicians should be mindful of a differential diagnosis.
2. In a UK published cohort (n=13), critical illness in the paediatric population with pandemic (H1N1) 2009 Influenza appears mostly to affect children over 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).<sup>1</sup> 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 CDC in the US 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.<sup>2</sup>
3. Most, but not all, severely ill children have co-morbidities. Severe neuro-developmental problems (often associated with chronic respiratory diagnoses) and immunodeficiency are noted.<sup>1,3</sup>
4. In the small numbers to date in the UK, chronic respiratory disease has been a feature in some hospitalised children but not the critically ill group. This contrasts with the picture in seasonal flu where respiratory disease is a common co-morbidity.<sup>1,3</sup>
5. The predominant presentation is as a respiratory illness with cough and dyspnoea. Fever, though not universal in the hospitalised population, has occurred in all those admitted to critical care to date.<sup>1,3</sup>
6. Shock has also been a feature of critically ill children presenting with pandemic (H1N1) 2009 influenza to a greater degree to which it is seen in seasonal influenza cohorts.<sup>1</sup>
7. Severe gastrointestinal disease (nausea, vomiting, diarrhoea, abdominal pain) is a recognised presentation of pandemic influenza.
8. Amongst paediatric cases, while infrequent, new neurological disease (encephalitis with coma or status epilepticus) can be a feature of the presentation and may be the sole symptoms.<sup>4</sup>
9. Pandemic (H1N1) 2009 influenza may tip some children with chronic sub-clinical disease to present, for example with diabetic keto-acidosis.<sup>1</sup>
10. Laboratory confirmed secondary infection was seen in 10 of the 23 paediatric deaths reported to the CDC in the US who had microbiology results available.<sup>2</sup>
11. Consideration should be given regarding empirical cover with broad spectrum antibiotics in all hospitalised cases.
12. Consideration and exclusion of other pathologies (e.g. meningococcal sepsis, herpes encephalitis, group A streptococcal infections) must be part of the assessment of critically ill children, since these will continue to present during an influenza pandemic.



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

- Hypoxaemia ( $SpO_2 < 94\%$ ) resistant to high flow oxygen therapy.
- Worsening respiratory failure characterised by: severe, recurrent, prolonged apnoea requiring resuscitation; worsening tachypnoea with gasping or grunting; or a rising  $pCO_2$  on sequential blood gas analysis.
- Cardiovascular collapse/shock that does not respond to a fluid resuscitation (equal to or greater than a total of  $40 \text{ ml/kg}^{-1}$  of 0.9% saline or Hartmann's).
- Encephalitis with coma ( $GCS < 9$ ) or seizures requiring intubation for airway control.

## Respiratory disease

1. 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.
2. Critical care outreach and early warning scoring systems may be helpful in identifying patients who should be considered for escalation.
3. 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.<sup>1</sup> 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.
4. Non-invasive ventilation (NIV) has been used but appears to confer no advantage in the ARDS group.
5. Children will present during the pandemic with a bronchiolitic picture and type 2 respiratory failure and this may be due to pandemic H1N1 2009 influenza, hRSV 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 population. NIV can also be considered in the convalescent phase.
6. 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 ( $FiO_2 > 0.8$ ) or high pressure ( $PIP > 30\text{cmH}_2\text{O}$ ) ventilation. Multi-organ failure does not preclude ECMO therapy.
7. 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.

8. 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

1. Shock is recognised at presentation (8/13 in the UK series) 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.
2. Aggressive fluid resuscitation and early use of inotropes in a targeted fashion (urine output,  $SvO_2$ , lactate) is appropriate.
3. High dose steroids are associated with increased mortality in sepsis.<sup>7,8,9</sup>
4. 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.<sup>10</sup>
5. 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.<sup>11</sup>
6. Catecholamine resistant shock occurred in four of the eight paediatric UK cases. Vasopressors and replacement dose steroids have been used in this context.
7. Multi-organ failure is not a contraindication to ECMO (see above).
8. Myocarditis has been described in children. 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.
9. Early echocardiography in shocked children is recommended to exclude this as a cause of circulatory failure.

## Neurological disease

1. Seizures and status epilepticus have been seen as the presenting feature of pandemic (H1N1) 2009 influenza in children.<sup>4</sup>
2. Seizure control and airway management should follow standard guidelines.
3. CT scans should be considered as per usual practice to exclude other pathology. This has revealed other pathology in pandemic (H1N1) 2009 influenza (for example cerebral oedema and infarction).<sup>4</sup>
4. Lumbar puncture has a role in excluding other causes of meningoencephalitis ( for instance herpes simplex



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virus types I & II). Pandemic H1 RNA PCR may be positive on CSF.

5. The empirical use of acyclovir should be considered for all infants with a neurological presentation pending a HSV PCR result on CSF.
6. Non-specific EEG abnormalities have been described.
7. The prognosis in isolated neurological presentation where described outside the critical care setting appears good.<sup>4</sup> Acute neurological symptoms should not limit other therapy, except where clear evidence of an irreversible deficit exists.
8. 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.<sup>5</sup>

## Renal replacement therapy

1. Renal replacement therapy has been required by critically ill adults with pandemic (H1N1) 2009 infection.
2. Paediatric experience is limited; at the time of writing one ECMO case in the UK has been treated with continuous veno-venous haemofiltration (CVVH).

## Microbiology and Infection control

1. Local guidelines for infection control should be followed.
2. 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. Diligence in hand hygiene between patients must be maintained.
3. Immunofluorescence is not sufficiently sensitive for detection and so PCR should be used.
4. Virus detection by PCR from the upper and lower respiratory tract can vary during the course of the illness. In other respiratory viral disease affecting children detection from the upper and lower respiratory tract can vary during the course of illness. For example samples from nose and throat may be negative when lower tract secretions are still positive. In intubated children it is therefore preferable to send endotracheal aspirates (ETA) or non-directed bronchoalveolar lavage (NDBL) for analysis.
5. 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.
6. NIV is potentially an infectious aerosol generating procedure and full PPE should be worn when caring for patients. Nosocomial spread has been reported in this context associated with sub-optimal PPE usage.

7. Several cases have required high frequency oscillatory ventilation (HFOV). This may cause environmental contamination when oscillators are used without exhaust scavenging or filters. No cases of infection of clinical staff or nosocomial infection have been reported in this context.
8. Serial sampling should be considered in discussion with the local laboratory. Repeat testing in the context of ongoing/worsening clinical picture may have a utility with regard to guiding duration of prolonged treatment with oseltamivir, resistance testing or consideration of alternative antivirals.
9. When deterioration occurs viral and bacterial screening should be repeated to screen for other pathogens (endemic seasonal viruses, which may co-infect, and bacteria).
10. In children with ongoing respiratory symptoms infection control should be maintained.

## Antimicrobial therapy

1. Concurrent bacterial infection has been reported with pneumococcus, staphylococcus and group A streptococcus.
2. Empirical treatment with broad spectrum antibiotics is appropriate in the setting of severe pandemic (H1N1) 2009 influenza respiratory or multi-organ failure.
3. Treatment with oseltamivir should be started on clinical grounds while awaiting test results.
4. Oseltamivir dosing should follow current national guidelines.
5. Liaise with local experts for most up-to-date antiviral guidance.
6. Some clinicians have doubled the dose in older critically ill children; however the risks and benefits of this are unclear.
7. Oseltamivir dose should not be doubled in children under the age of one year.
8. Concerns have been raised about enteral absorption of oseltamivir. This has not appeared to be a common problem in the critically ill population to date.
9. The use of intravenous zanamivir is unproven. However, experts may consider using it in certain circumstances. Under compassionate use an intravenous preparation of zanamivir has been used in a case of suspected poor enteral absorption.<sup>6</sup> No data is available for children.



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