

Summary recommendations

- 1. A full blood count with differential, urea, creatinine and electrolytes and liver enzymes and a blood culture should be done in all severely ill children.**
- 2. A CXR should be performed in children who are hypoxic, have severe illness or who are deteriorating despite treatment.**
- 3. Pulse oximetry should be performed in every child being assessed for admission to hospital with pneumonia**

13.1 Are blood tests useful?

A low WBC is common in influenza A in children. (WBC<4 in 8-27%(96;105), WBC <5 in 24%(117)) with a lymphopenia (<1.5 in 41%(120);<1.0 in 40%(105)). In contrast a raised WBC (>15) is found in only 8-12% of cases.(96;105)

In the H5N1 cases reported from Vietnam(55) all 7 children had WBC < 4.0 (mean 2.44) and 6/7 had a lymphopenia <1.0 (mean 0.66). Six of the 7 children died. In contrast only 2 of the 7 children reported from Hong Kong died but they were both leukopenic and lymphopenic. The survivors had a mean WBC of 12.44 and lymphocyte count of 3.11.(54) Four of 5 cases reported from Thailand were lymphopenic.(121)

In Influenza A thrombocytopenia (<100) is found in 5-7%.(105;117) Thrombocytopenia was found in 4 /7 H5N1 Vietnamese children.(55)

Liver transaminases are raised in 27% Influenza A(120) and were raised in 6/6 of those measured in Hong Kong H5N1 outbreak(54) and 5 /6 in those measured in Vietnam.(55)

C-Reactive Protein (CRP) is unhelpful in influenza with values <10 in 55%;(117) <20 in 72%(96) and >80 in only 5%.(96)

The CD4/CD8 ratio was inverted in the 2 children and 3 adults in whom it was measured in the Vietnam outbreak (mean 0.7 R 0.59-1.08) Two of these patients survived. (55)

Recommendation

- A full blood count with differential, urea, creatinine and electrolytes and liver enzymes and a blood culture should be done in all severely ill children.**

13.2 When to do a chest radiograph?

One of the largest studies of the value of chest radiography was undertaken in children aged between 2 months and 5 years with community acquired pneumonia managed as outpatients with time to recovery as the main outcome.(122) Chest radiography did not affect the clinical outcome in these children with acute lower respiratory infection. This lack of effect was independent of clinicians' experience. There are no clinically identifiable subgroups of children within the WHO case definition of pneumonia who are likely to benefit from a chest radiograph. The authors concluded that routine use of chest radiography was not beneficial in ambulatory children aged over 2 months with acute lower respiratory tract infection (LRTI.)

13.2.1 Observer agreement on radiographic signs of pneumonia

Clinicians basing the diagnosis of lower respiratory infections in young infants on radiographic diagnosis should be aware that there is variation in intraobserver and interobserver agreement among radiologists on the radiographic features used for diagnosis. There is also variation in how specific radiological features are used in interpreting the radiograph. A recent study on standardization of CXR interpretation in paediatric pneumonia illustrates the importance of standardised training.(123) The cardinal finding of consolidation for the diagnosis of pneumonia appears to be highly reliable(124) and reasonably specific for bacterial pneumonia (74% of 27 patients with alveolar shadowing had bacterial proven pneumonia)(125) but overall chest radiography is too insensitive to be useful in differentiating between patients with bacterial pneumonia and those whose pneumonia is nonbacterial.(126;127)

In the context of an influenza pandemic a CXR will not distinguish viral pneumonia from viral illness with bacterial superinfection and all children with signs of pneumonia should be treated with antibiotics.

Recommendation

- **A CXR should be performed in children who are hypoxic, have severe illness or who are deteriorating despite treatment.**

13.3 Who should have pulse oximetry?

Oxygen saturation (SaO₂) measurements provide a noninvasive estimate of arterial oxygenation. Pulse oximetry will be a key tool in assessment and management and it is essential that it is used correctly and that users are aware of the possibility of artefactually low readings. The oximeter appears easy to use and requires no calibration. However, it requires a pulsatile signal from the patient. It is also highly subject to motion artefacts.

To obtain a reliable reading:

1. The child should be still and quiet
2. When using paediatric wrap around probes, the emitting and receiving diodes need to be carefully opposed
3. A good pulse signal (plethysmograph) should be obtained
4. Once a signal is obtained, the saturation reading should be watched over at least 30 seconds and a value recorded once an adequate stable trace is obtained

Recommendation

- **Pulse oximetry should be performed in every child being assessed for admission to hospital with pneumonia**

Summary Recommendations

(I) Early pandemic recommendations. (UK Alert levels 1-3)

A. Virology – all children

Nasopharyngeal aspirate or nose and throat swabs

B. Bacteriology – children with influenza related pneumonia

- Blood culture (before antibiotic treatment is commenced)
- Sputum samples obtained from older children
- Paired serological examination for influenza/other agents.

(II) Established pandemic recommendations (UK Alert level 4)

A. Virology – not routinely recommended

B. Bacteriology – children with influenza related pneumonia

- Blood culture (before antibiotic treatment is commenced)
- Sputum samples obtained from older children
- Paired serological examination for influenza/other agents

To be read in conjunction with Adult guidelines (section 7).

14.1 Introduction.

As with adults, the extent of virological and microbiological investigations undertaken in children should vary according to the stage of the pandemic and additionally according to the severity of an individual case. It should be noted however, that the clinical features of influenza in children are less characteristic than in adults (see section 1) and the need for special diagnostic tests is therefore greater.(96;128;129) A respiratory panel including influenza A and B, RSV, adenovirus, rhinovirus and parainfluenza 1,2,3 should be standard. The clinical features of human metapneumovirus infection may also be similar but current laboratory tests are limited.(120) Which tests are performed will vary according to the local laboratory but might include rapid antigen tests, immunofluorescence, culture, RT-PCR and serology. See Health Protection Agency guidance for further details.

14.2 Rapid influenza tests.

The utility of such tests has been demonstrated in studies where rapid knowledge of a diagnosis of influenza (within 10 minutes) has been shown to have an impact on clinicians` behaviour with respect to antibiotic use, performance of other tests and admission to hospital.(130;131) It may be imagined that in a pandemic situation such a test could result in earlier use of antiviral therapy and a more rational approach to hospital admission and to prophylaxis of contacts. However, using a molecular reference standard one test was shown to have low sensitivity (44%) but high specificity (97%) suggesting that its role might better be to “rule in” influenza rather than “ruling it out”.(132) Similar conclusions have been made with other commercial rapid tests.(133;134) As a reflection of this rapid antigen tests were positive in only 2 of 6 patients with avian influenza A (H5N1).(55)

14.3 Bacteriology

The need for bacteriological tests in cases of influenza with pneumonia is also logical and the range of pathogens similar to adults(36;103;135-139) except that legionella is extremely unlikely to occur in a previously healthy child and legionella-specific antigen testing is therefore unnecessary. The urinary pneumococcal antigen tests in children may lack both sensitivity and specificity and should be interpreted with care.(140;141) Sputum collection in children is also unreliable although in older children (eg > 12 years) it may be possible and should be handled as indicated for adults.

(I) Recommendations - Early pandemic (UK Alert levels 1-3)

A. Virology – all children

- **Nasopharyngeal aspirate or nose and throat swabs in virus transport medium should be collected from all patients and submitted to the local laboratory. The relevant laboratory should be notified of the suspected diagnosis and there should be close liaison over sample collection, handling and transport.**
- **Rapid testing by direct immunofluorescence or rapid EIA test, virus culture and/or PCR should be undertaken according to local availability and/or referred to an appropriate laboratory. Testing for influenza A and B, RSV, adenovirus, rhinovirus and parainfluenza 1,2,3 should be standard.**
- **If presentation is more than 7 days after onset of illness, an ‘acute’ serum (2-5 ml clotted blood) should be collected and a ‘convalescent’ sample (2-5 ml clotted blood) obtained after an interval of not less than 7days. The two sera should be examined serologically for evidence of recent influenza infection.**

B. Bacteriology – children with influenza related pneumonia

- **The following bacteriological tests should be performed:**
 1. **Blood culture (before antibiotic treatment is commenced)**
 2. **Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from older children who:
are able to expectorate purulent samples, *and*
have not received prior antibiotic treatment.
Sputum samples should be transported rapidly to the laboratory.**
 3. **Paired serological examination for influenza/other agents. Acute serum should be collected and a ‘convalescent’ sample obtained after an interval not less than 7days (both 2-5 ml clotted blood) and the two sera stored for subsequent testing.**

(II) Recommendations - Established pandemic (UK Alert level 4)

A. VIROLOGY – Not routinely recommended.

B. BACTERIOLOGY - children with influenza related pneumonia

Specific investigations should include:

1. **Blood culture, before antibiotic treatment is commenced**
2. **Sputum Gram stain, culture and antimicrobial susceptibility tests on samples obtained from older children who:
are able to expectorate purulent samples, *and*
have not received prior antibiotic treatment.**

Sputum samples should be transported rapidly to the laboratory.

3. Paired serological examination for influenza/other agents. 'Acute' serum should be collected and a 'convalescent' sample obtained after an interval not less than 7 days (both 2-5 ml clotted blood) and the two sera stored for subsequent testing.
4. In an intubated patient tracheal or endotracheal aspirate samples, should be sent for Gram stain, culture and antimicrobial susceptibility testing as well as viral testing (listed above).

DRAFT FOR CONSULTATION

Summary recommendations

1. Where possible children should be cohorted using rapid virological tests
2. Patients whose oxygen saturation is 92% or less while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92%.
3. When children are unable to maintain oral intake supplementary fluids should when possible be given by the enteral route. Intravenous fluids in those with severe pneumonia should be given at 80% basal levels.
4. Children can be safely discharged from hospital when
 - Child is clearly improving
 - is physiologically stable
 - can tolerate oral feeds
 - respiratory rate is < 40/min (<50/min in infants)
 - awake oxygen saturation is >92% in air.

15.1 Introduction

During an influenza pandemic children are likely to be admitted to hospital because of the severity of their disease and its complications or because of the impact of influenza on preexisting disorders such as cardiac, respiratory or neurological disease. Management of preexisting disorders is outside this guideline.

The most common reason for admission is likely to be

1. Lower respiratory tract disease with either a viral or bacterial or mixed pneumonia.
Other reasons for admission include
2. Severe gastroenteritis
3. Cardiac disease – viral myocarditis
4. Encephalitis

15.2 Triage

Children should be triaged to ward or HDU/PICU after severity assessment (section 12)

15.3 Cohorting

An influenza pandemic is likely to occur in the winter months when other winter viruses responsible for paediatric morbidity and hospital admission are circulating (such as RSV and adenovirus) Particularly in the early stages of a pandemic (UK Alert levels 1-3) it will be important to use rapid virological tests in an attempt to cohort influenza positive and RSV positive infants separately and to separate from other patients. See Health Protection Agency guidance.

15.4 Who needs oxygen?

Hypoxic infants and children may not appear cyanosed. Agitation may be an indication of hypoxia. Patients whose oxygen saturation is less than 92% while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92%. Nasal cannulae do not deliver a FiO₂ more than around 40% even at flow rates of 2l/min in infants and 4l/min in older children. Alternative methods of delivering higher concentrations of humidified oxygen such as a head box or a venturi face mask may be necessary. If SaO₂ >92% cannot be maintained with FiO₂ of 60% then additional support such as CPAP, BiPAP or intubation and ventilation should be considered.

Recommendation : Patients whose oxygen saturation is 92% or less while breathing air should be treated with oxygen given by nasal cannulae, head box, or face mask to maintain oxygen saturation above 92%.

15.5 Who needs fluids?

Children who are unable to maintain their fluid intake due to breathlessness, fatigue or gastroenteritis need fluid therapy. Where possible additional fluid should be by the enteral route and where nasogastric tube feeds are used, the smallest tube should be passed down the smallest nostril to minimize effects on respiratory status. Severely ill children may need intravenous fluids and if the child is in oxygen therapy intravenous fluids should be given at 80% basal levels (to avoid complications of inappropriate ADH secretion) and serum electrolytes should be monitored.

15.6 What monitoring is necessary?

The monitoring will depend on the child's condition. Severely ill children will need continuous monitoring of heart rate, respiratory rate, oxygen saturation and neurological status. All children on oxygen therapy should have four hourly monitoring including oxygen saturation.

15.7 Who needs physiotherapy?

Chest physiotherapy is not beneficial in previously healthy children with pneumonia. Children with underlying conditions such as cystic fibrosis or neuromuscular weakness will benefit from intensive physiotherapy

15.8 Management of fever and pain

Children with influenza are generally pyrexial and may have some pain, including headache, chest pain, arthralgia, abdominal pain, and earache from associated otitis media. Pleural pain may interfere with depth of breathing and may impair the ability to cough. Antipyretics and analgesics can be used to keep the child comfortable and to help coughing.

15.9 When can children be safely discharged from hospital?

In a pandemic situation there will be great pressure on hospital beds. All children should be assessed for discharge at least twice daily. Children should not remain in hospital if they are receiving therapy that could be given in the community. In previously healthy children suitable discharge criteria would be:

1. child is clearly improving
2. is physiologically stable
3. can tolerate oral feeds
4. respiratory rate is < 40/min (<50/min in infants)
5. awake oxygen saturation is >92% in air.

15.10 Who needs follow-up?

Most children will make an uneventful recovery and not require follow up. Those with a prolonged illness may be followed up by their general practitioner. Only children with severe disease and/or at high risk of sequelae need hospital follow up. Children with lobar collapse should have a follow up CXR. Follow up CXRs after acute uncomplicated pneumonia are of no value where the patient is symptomatic.(142;143)

Summary recommendations.

1. In the setting of a pandemic, children should only be considered for treatment with antivirals if they have **all** of the following:
 - an acute influenza-like illness (see definition in clinical section)
 - fever ($>38.5^{\circ}\text{C}$) *and*
 - been symptomatic for no more than 2 days.
2. Oseltamivir is the antiviral agent of choice.
3. In children who are severely ill in hospital oseltamivir may be used if the child has been symptomatic for <6 days.

To be read in conjunction with Adult guidelines (section 9).

16.1 Introduction

Five antiviral agents are theoretically available for the therapy of influenza in children: the M2 ion channel inhibitors amantadine and rimantadine (both administered orally and for influenza A only), the neuraminidase inhibitors oseltamivir (administered orally) and zanamivir (administered through an inhaler), and ribavirin (aerosolised).

16.2 Amantadine/rimantadine

The limitations of amantadine and rimantadine are detailed in the adult section, particularly in the context of a pandemic where resistance may already be present.(144) Both have been shown to be effective in the treatment of influenza A in children.(145) Concerns exist about the development of resistance during therapy for both agents.(145;146) A household study showed that treatment and prophylaxis with rimantadine resulted in rapid selection and transmission of drug resistant virus.(147)

16.3 Neuraminidase inhibitors

In a double-blind randomised, placebo controlled study 217 children (1-12 years of age) received oseltamivir with a resultant reduction in the median duration of illness, otitis media and need for antibiotic prescriptions.(70) The most common side effect was vomiting (5.8%). A systematic review and meta-analyses published in 2003 which included studies up to December 2001 included only 2 studies of zanamivir and 1 study of oseltamivir(70) in which these drugs were administered for treatment of influenza A or B in children < 12 years of age.(148) The reduction in the median time to alleviation of symptoms for influenza positive children when compared with placebo was 1.0 day (95% CI 0.4-1.6) for zanamivir and 1.5 days (0.8-2.2) for oseltamivir. Across all ages a 29% (10-44) relative reduction in complications requiring antibiotics was observed for zanamivir and for children specifically a 35% relative reduction was observed for oseltamivir. This was updated through to December 2002 in a Cochrane review.(149) Using its search criteria it identified 2 trials of oseltamivir (1 in healthy children(70) and 1 in children with asthma which was later published(150) and only 1 with zanamivir. Its conclusions were therefore the same with respect to median illness duration in healthy children. A significant reduction in complications (otitis media) was noted for oseltamivir while a trend to benefit was seen for zanamivir.(149) Vomiting was significantly more common among oseltamivir recipients than placebo recipients (15% vs. 9%). The review noted that there may be a difference in efficacy according to serotype with oseltamivir showing a significant reduction in time to resolution for influenza A (34%) but not B (8.5%).(149) With respect to children with asthma there was a trend to reduction in time to freedom from illness for oseltamivir recipients but this did not reach statistical significance. Oseltamivir appeared to result in a more rapid improvement in pulmonary function, and was well tolerated in children with asthma.(149;150) The Cochrane review concluded that oseltamivir was the preferred drug as it has shown a benefit with regard to secondary complications. It also concluded that there was no evidence of

benefit in at-risk children (i.e. asthma). From the perspective of pandemic use however, it should be noted that there was no evidence of harm in this group.

With regard to dosing of oseltamivir, pharmacokinetic studies have suggested that young children clear the drug faster than older children, adolescents and adults and therefore need higher doses.(151;152) The major practical issue with regard to zanamivir is its mode of administration limiting its use to children over the age of 5 years (FDA guidance: over 7 years of age).(149)

The development of resistance to oseltamivir in children may be more common than appreciated and more common than seen in adults. In one study resistance mutations were documented in 18% of 50 children.(152) This has implications for widespread use in a pandemic situation.

One particular issue with regard to paediatric use of oseltamivir is the apparent age limitation on its license (i.e. not for children < 1 year of age). This is particularly important because during epidemic years of all children with influenza it is children < 6 months of age who are most likely to be hospitalised.(153) The basis for this exclusion appears to be that rat data have shown high mortality in infant rats at 7 days of age when given a dose of 1000mg/kg together with high brain levels of oseltamivir, assumed to reflect the immature blood-brain barrier at this age. This is reflected in product literature and an FDA alert although there are no published data. As a result there are few human data in this age group as it was felt that it would be difficult to monitor CNS toxicity in this age group. However, because of a fear of encephalopathy due to influenza in young children Japanese paediatricians have been using it in infants and data on 102 consecutive infants from Japan revealed no encephalopathy or mortality in recipients.(154) A second Japanese report has just been published where 47 children <1year were treated (4mg/kg/day) showing similar efficacy for fever to a group of older children and no serious adverse effects.(155)

There are no data on the effectiveness of Oseltamivir if given more than 2 days from onset of illness. It is likely to be less effective and in particular to have little or no effect after 5-6 days of illness unless the child is immunosuppressed. Giving Oseltamivir to sick hospitalised patients is theoretically likely to decrease their infectivity and so may be useful but there are no data to support this.

16.4 Ribavirin

In a double blind placebo controlled study children hospitalized with influenza who had been ill ≤ 48 hours and who had a temperature ≥ 37.8 degrees C were randomised to receive either ribavirin or placebo. Sixty-two patients (35 in the placebo group, 27 in the ribavirin group) had a confirmed diagnosis of influenza. The time to reduction of temperature ≤ 38.3 degrees C for the ribavirin group was 8.9 hours compared with 22.6 hours for the placebo group ($p = 0.04$). There were no other differences detected between groups.(156) There have been no further published studies in the 11 years since this report thus ribavirin cannot be recommended at this time.

Recommendations

- **In the setting of a pandemic, children in the community should only be considered for treatment with antivirals if they have all of the following:**
 1. **an acute influenza-like illness (see definition in clinical section)**
 2. **fever ($>38.5^{\circ}\text{C}$) and**
 3. **been symptomatic for 2 days or less.**

- **Oseltamivir is the anti-viral agent of choice.**

Treatment Schedule for children over 1 year.

Body weight 15kg or under ie <3 years : 30mg every 12 hours;

Body weight 16-23kg i.e. < 7 years: 45mg every 12 hours;

Body weight 24kg and over i.e. > 7 years : 75mg every 12 hours .

- **In children who are severely ill in hospital oseltamivir may be used if the child has been symptomatic for <6 days.**

Oseltamivir may be considered for the treatment of infants < 1 year of age, especially those with severe influenza. This would need to be done following appropriate discussion with the parents highlighting the concerns from the animal data and the relative paucity of human data in this age group.

DRAFT FOR CONSULTATION

Summary recommendations

1. Children a) who are at risk of complications of influenza or b) with disease severe enough to merit hospital admission during an influenza pandemic should be treated with an antibiotic that will provide cover against *S pneumoniae*, *Staph aureus* and *H influenzae*.
2. For children under 12 years co-amoxiclav is the drug of choice. Clarithromycin or cefuroxime should be used in children allergic to penicillin. For children over 12 years doxycycline is an alternative.
3. Oral antibiotics should be given provided oral fluids are tolerated.
4. Children who are severely ill with pneumonia complicating influenza should have a second agent added to the regime (eg clarithromycin or cefuroxime) and the drugs should be given intravenously to ensure high serum and tissue antibiotic levels.

These recommendations are based on the most likely anticipated scenarios but may need to be modified in the light of emerging information in an actual pandemic

17.1 Who should get antibiotics?

Secondary bacterial infections particularly pneumonia and otitis media are common in children with influenza. A case control study during an outbreak of severe pneumococcal pneumonia demonstrated that patients with severe pneumonia were 12 times more likely to have had an influenza like illness and 4 times more likely to have positive influenza serology than controls. (103) Infections with *Staphylococcus aureus* and *H influenzae* are also more common during influenza outbreaks.

A randomized controlled trial of antibiotics in 85 children aged 4 months to 11 years presenting with influenza like symptoms during an influenza epidemic showed a decreased incidence of pneumonia in the antibiotic treated group. (2.4% vs 16.3% p=0.031) (157) There was no change in duration of fever or incidence of acute otitis media. Interestingly only 1/7 of the cases of pneumonia in the placebo group was thought to be bacterial. The authors postulated that as bacterial proteases facilitate propagation and pathogenesis of influenza in a mouse model that decreasing bacterial numbers and hence protease levels in the lung may decrease viral pneumonia.

Another randomized trial of cephalosporins vs macrolides in 365 Japanese children with influenza like symptoms showed faster alleviation of fever (3.8+/-1.4 vs 4.3+/-1.4 days p=0.006) in the macrolide group and a decrease in number with CXR evidence of pneumonia (2 vs 13 cases p=0.002 ; 14/15 had interstitial changes). (158) The authors postulate that anti-inflammatory effects of macrolides may be responsible.

Recommendation

- Children a) who are at risk of complications of influenza and b) Children with disease severe enough to merit hospital admission during an influenza pandemic should be treated with an antibiotic that will provide cover against *S pneumoniae*, *Staph aureus* and *H influenzae*.

17.2 Which antibiotic?

The antibiotics of choice must cover the likely pathogens as above. Data from HPA 2004 indicate that in the UK <2.5% of *S pneumoniae* strains are penicillin resistant but 14.1% are erythromycin (macrolide) resistant. Similarly 14% of methicillin susceptible *Staph aureus* were erythromycin resistant. Only 76% of *H. influenzae* are susceptible to amoxicillin but >94% are susceptible to co-amoxiclav. There may be local variations to this data and clinicians should consult with their local microbiology department.

Recommendation

- For children under 12 years co-amoxiclav is the drug of choice. Clarithromycin or cefuroxime should be used in children allergic to penicillin. For children over 12 years doxycycline is an alternative.

17.3 What if the pathogen is known?

Rarely a blood culture or pleural tap will provide the pathogen. The antibiotics should then be specifically tailored eg benzyl penicillin iv or oral amoxicillin for *S. pneumoniae* and flucloxacillin or clindamycin for *S. aureus*.

17.4 Oral or intravenous?

A recent randomized controlled trial of the equivalence of oral amoxicillin vs iv benzylpenicillin in 252 children admitted to hospital with community acquired pneumonia showed no difference in duration of illness or complications.(159) Oral antibiotics should be given provided oral fluids are tolerated.

17.5 Antibiotic choice for severe or complicated pneumonia?

Children who are severely ill with pneumonia complicating influenza should have a second agent which provides good cover for gram positive organisms added to the regime (eg clarithromycin or cefuroxime) and the drugs should be given intravenously to ensure high serum and tissue antibiotic levels.

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