MANAGEMENT OF INFLUENZA-LIKE ILLNESS DURING AN INFLUENZA PANDEMIC IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISORDERS

Influenza virus infection

- Influenza is a clinical syndrome which in humans is the result of infection with influenza virus types A, B or C. Influenza B and C viruses infect only humans. Influenza A can also infect pigs, birds and horses. Infectivity, replication and transmission are determined, in part, by two cell surface glycoproteins (haemagglutinin and neuraminidase). The effectiveness of adaptive immune responses against influenza viruses is determined by natural minor (antigenic drift) or major (antigenic shift) changes in these glycoproteins. Antigenic shift is responsible for the widespread pandemics which occur intermittently. Antigenic drift occurs more commonly and is responsible for the more localised outbreaks of flu which occur year to year.
- Infection can occur as sporadic individual infections, local outbreaks, widespread epidemics or worldwide pandemics.
- Influenza is a short-lived infection with respiratory and systemic symptoms which vary widely between individuals but, in the uncomplicated state, generally include dry cough and other coryzal symptoms, malaise, fever, rigors, headache, anorexia, photophobia, nasal congestion, sore throat and myalgia. Recognised disease complications include tracheitis, bronchitis, pneumonia (primary or secondary bacterial), otitis media, myositis and, more rarely, myocarditis, paricarditis, myoglobinuria, toxic shock syndrome, parotitis, encephalitis, encephalopathy and other neurological problems. Associated fatalities, when they occur, are usually the result of viral or secondary bacterial pneumonia.
- Infection is usually spread by aerosol/droplet inhalation with an incubation of 48-72 hours.
- As many different kinds of respiratory viruses can cause symptoms similar to those of flu, in the absence of definitive virological evidence of influenza virus infection the clinical scenario encompassing the signs and symptoms above is referred to as ‘influenza-like illness’ or ILI.
- an effective adaptive immune response against influenza virus infection involves production of neutralising antibody against haemagglutinin and neuraminidase along with specific IgA and an intact complement system. Specific T cell reactivity is also likely to play an important role through assistance for antibody production and perforin-mediated cytotoxicity.

Influenza pandemics

- Seasonal human flu typically affects 1-15% of the UK population each winter and leads to around 12,000 excess deaths.
- Human flu is highly infectious before patients develop definite symptoms. This causes major problems in control of spread of infection.

- Pandemics are triggered by a major shift in the influenza virus surface haemagglutinin protein antigens. This occurs relatively rarely. Minor antigenic drift in neuraminidase accounts for year-to-year variability in prevalent strains.
- Recent recorded pandemics have occurred in:
    - 1918/19: 'Spanish Flu, H1N1 virus, estimated 250,000 excess UK deaths
    - 1957/58: 'Asian' Flu, H2N2 virus, 33,000 excess deaths
    - 1968/69: 'Hong Kong' Flu, H3N2 virus, 30,000 excess deaths

  It is expected that another worldwide pandemic is now due/overdue
- There is significant public confusion, misunderstanding and inappropriate extrapolation over the potential for a human influenza virus pandemic and the risks posed to humans by avian influenza viruses (principally and currently H5N1 virus in respect of the latter). Lack of sustained human-to-human transmission of H5N1 suggests that, although the virus can be transmitted to humans and can cause fatalities, it does not have the capacity (at least at present) to cause a human pandemic.
- Conservative modelling suggests that 25% of the UK population (>14 million) would become ill during a human influenza pandemic with 50,000 excess deaths during initial and successive pandemic waves.
- A new pandemic would be expected to spread throughout the UK in 1-2 weeks and would be active for 3-5 months, peaking at week 6.
- Recently developed guidelines propose:
    - targeted treatment with antiviral drugs (principally oseltamivir) for patients within 48 hours of developing an influenza-like illness during a pandemic (with the aims of shortening symptom duration, reducing infectivity and preventing secondary complications).
    - Early treatment with prophylactic antibiotics for high risk patients who have influenza-like symptoms to prevent or reduce the clinical effects of secondary bacterial lung infection.
- Antiviral agent stocks are currently available for only 25% of the population.
- There is little in the way of direct evidence to allow accurate risk assessment for patients with primary immunodeficiency (PID) or to guide practice in the management of influenza during a pandemic at a population, cohort or individual level.

Management of ILI in PID Patients

Strategic aims of existing guidelines are to limit domestic spread and minimise adverse effects on health, society and the economy with recommendations intended to operate a) at a population level or b) at the level of healthcare practitioners, regardless of specialisation, who may be involved in the management of patients with influenza. This document is intended to provide additional information and specific recommendations for centres and practitioners involved in the care of patients with PID disorders.

Patients with PID should be considered an 'at risk' group during an influenza pandemic. Clinical management measures can be organised under the following broad headings:

A) General Actions for UK Primary Immunodeficiency Centres
B) Prevention Measures (infection control and vaccination)
C) Prophylactic Treatment with Antiviral Agents
D) General and Symptomatic Treatment Measures
E) Specific Treatment Measures in Acute ILI

A) General Actions for UK Primary Immunodeficiency Centres

Recommendations:

- Ensure ready lines of communication for help and advice between patients and PID Centre staff.
- Recommend annual influenza immunisations for all PID patients and their household contacts (see below).
- Ensure ready availability of prophylactic antibiotics for self-initiated use in PID patients with established lung disease (see below).
- Ascertain up-to-date situation regarding local availability of anti-viral drugs.
- Advise patients about symptoms of influenza and actions to take in the event of contact with influenza or development of symptoms. In particular, emphasise importance of contact (ideally by indirect methods, such as telephone, if possible) with General Practitioner or local Immunology team early after exposure or symptoms (and within 48 hours at latest).
- Advise General Practitioner to contact local Immunology team if consulted by PID patient concerning influenza symptoms/exposure.
- Ensure availability of specialist advice to acute hospital medical teams for care decisions on PID patients.
- Monitor relevant local and national agencies regularly to ascertain level of influenza activity e.g. Health Protection Agency (http://www.hpa.org.uk/).

B) Prevention Measures

Relevant actions comprise infection control measures and vaccination of PID patients.

Infection control is aimed at reducing viral transmission.

Vaccination: effective vaccines must contain haemagglutinin and neuraminidase antigens of recently isolated virus strains. Specific virus contents of vaccines require to be reviewed annually and changed to encompass new virus variants as they occur. Vaccines may contain whole inactivated virus or viral sub-units and produce effective immunity in 60-90% of non-PID cases. Live vaccines are not currently available for routine, widespread clinical usage. The efficacy of vaccination in patients with primary immune deficiency is unknown but likely to be sub-optimal. **Nevertheless, the potential for at least a degree of useful T cell priming means that vaccination should be considered as a potentially beneficial management tool in PID patients.**

Recommendations (infection control):

- When healthy, avoid high-risk environments such as hospital or General Practice surgeries other than for unavoidable or important reasons (e.g. to receive scheduled treatments such as regular immunoglobulin replacement or immunisations or to collect medicines) during the surge phase of a pandemic.

- Where possible and practical, consider segregation/separation of patients with ILI symptoms and healthy patients who are attending for Day Case procedures or outpatient appointments.

- Where possible and practical, symptomatic patients should be asked to stay at home or at their normal place of residence (voluntary isolation and quarantine). In these circumstances, patients should have ready access to specialist advice by telephone or other indirect methods (e.g. e-mail). Where hospital attendance is necessary for Day Case assessment/treatment or because of acute, severe illness patients may require a letter or warning/priority card to access secondary care facilities (such measures will require to be interfaced with/co-ordinated with local institutional pandemic triage arrangements).

- Provide advice on/institute basic personal awareness and personal hygiene measures (Appendix 1).

Recommendations (vaccination):

- UK PIN consensus strategy is to recommend routine, annual influenza immunisation with inactivated virus for patients with primary immune deficiency. Household contacts and family members should also be immunised where possible to reduce the risk of household/social transmission. Priority immunisation with newly-developed vaccine strains, as available, during an influenza epidemic or pandemic is also recommended.

C) Prophylactic Treatment with Antiviral Agents

Antiviral agents comprise drugs in three categories: synthetic primary amines (amantadine, rimantadine), synthetic nucleosides (ribavirin) or neuraminidase inhibitors (oseltamivir, zanamivir). Oseltamivir has been selected by the UK Departments of Health as the antiviral drug agent of choice for national stockpiling and use during an influenza pandemic. In spite of this it seems unlikely that sufficient supplies will available, or made available, for either short or long-term prophylactic usage in asymptomatic patients in contact with an ILI during a pandemic, even in high risk groups. Development of prioritisation guidelines is anticipated. The manufacturers recommend the drug for prophylactic use only in patents aged 13 years or over who are not effectively protected by vaccination.

Recommendations (prophylactic antiviral therapy):

- In the (presumed unlikely) event that supplies become available for general or targeted (high-risk group) use as post-exposure prophylaxis for immediate contacts of domestic or social infection, oseltamivir should be administered to patients affected by PID disorders (>13 years of age only) in a dose of 75 mg once daily for 7 days (post-exposure prophylaxis), or for up to 6 weeks during an epidemic/pandemic (pandemic period prophylaxis), depending on availability.

D) General and Symptomatic Treatment Measures

Recommendations:

- Rest (or bed rest) until resolution of acute symptoms (generally 2-3 days)
- Analgesia for headache, myalgia and fever (avoiding salicylates in children)
- Encourage fluid intake
- Symptomatic adjuncts such as codeine (cough), topical decongestants, throat lozenges etc.

E) Specific Treatment Measures in Acute ILI

Oseltamivir

Usage of oseltamivir is intended to shorten symptom duration, reduce infectivity and prevent complications. Existing guidelines for usage of antiviral agents in the context of influenza indicate that treatment with neuraminidase inhibitors should only be considered if patients have all of the following:

- an acute influenza-like illness
- fever (>38^{o}C in adults or>38.5^{o}C in children)
- symptoms for 48 hours or less

Two relevant exceptions to these qualifiers are:

- Where patients are unable to mount an adequate inflammatory response (specifically including the immunocompromised) and should still be eligible for antiviral treatment despite lack of any documented fever and
- Immunosuppressed patients who may possibly benefit from antiviral therapy commenced later than 48 hours after the onset of a symptomatic ILI (there is no evidence to support, or to refute, this aspect of published guidance).

Oseltamivir is the agent of choice in both adults and children. Treatment should ideally be started within **48 hours** of onset of symptoms in all cases. Oseltamivir is likely to be ineffective or sub-optimally effective if start of treatment is delayed beyond 48 hours. The drug is licensed for treatment of influenza virus infection in patients of one year and

over (but only licensed for prophylactic use >13 years). Dosage should be adjusted in renal impairment.

Antibiotics

Antibiotics may be used at an early stage in high risk patients with ILI to prevent or ameliorate secondary bacterial (principally pulmonary) infection, though their usage, even in patients with chronic lung disease, is contentious.

Existing pandemic influenza guidelines support routine, early use of antibiotics:

a) In all patients at high risk of complications or secondary infection in the presence of lower respiratory features or worsening symptoms (recrudescent fever or increasing dyspnoea)

b) At first consultation with uncomplicated ILI-like symptoms in patients with COPD and/or other severe co-morbid disease

Guidance for antibiotic use in adults (all) with influenza in the community:

Patient group	Recommendation
Not complicated by influenza-related pneumonia:	
- previously well	Antibiotic not routinely required
- previously well but who have developed worsening symptoms	Consider antibiotic use
- Patient with COPD and/or other severe pre-existing disease	Strongly consider antibiotic use
Complicated by influenza-related pneumonia:	
- all patients	Antibiotics recommended

Adapted from Lim, WS. Thorax 2007; 62 suppl 1: 1-46

Taking this advice into account, UK PIN advises that antibiotics should be routinely used at an early stage for community, day-case or outpatient management of PID patients in combination with antiviral agents in the following circumstances:

a) PID disorder (any) + ILI + lower respiratory symptoms/recrudescent fever/increasing dyspnoea
b) PID disorder with associated background chronic pulmonary disease + ILI (complicated or uncomplicated) as from initial consultation
c) Children with PID + ILI, where special consideration should be given to usage of antibiotics (see recommendations below)

Most patients can be treated adequately with oral antibiotics. Duration of treatment will be determined by clinical response. For non-severe cases, whether treated in the community or in hospital, a minimum of seven days treatment with antibiotic is recommended.

Antibiotics may be used according to established local protocols or the following general guidance may be followed:

Preferred first line: co-amoxiclav or doxycycline
Alternative: clarithromycin/erythromycin or a fluroquinolone agent
Severe influenza-related pneumonia or the presence of bilateral chest signs (crackles) or pulmonary infiltrates on chest X-ray require hospital admission, treatment with parenteral antibiotics in combination and consideration of the potential presence of primary viral pneumonia.

E1 Treatment of Adults with PID

Patients should be referred from Primary Care, or self-refer, to their Immunology team if a) there is a worsening of their pre-existing PID disorder or b) if they develop an influenza-related complication. Close assessment and regular re-assessment may be required, as may hospital admission.

As pneumonia is the commonest influenza-related complication requiring hospital admission CURB-65 severity assessment (Appendix 2), developed by the British Thoracic Society, may be a useful tool, though unvalidated in this setting, to inform decision-making about the siting and circumstances of treatment, including hospital inpatient admission. This tool may supplement, but does not replace, clinical judgement.

Recommendations (specific treatment measures in a non-inpatient setting):

- Oseltamivir 75 mg b.d. for (minimum)5 days
- Antibiotic: If ILI + lower respiratory symptoms/fever recrudescence/dyspnoea
  OR
  chronic pulmonary disease + ILI (complicated or uncomplicated)
  : co-amoxiclav or doxycycline (first-line)
  : macrolide or fluroquinolone drug (alternative)
- Consider hospital admission in cases of:
  - worsening infection symptoms
  - severe pneumonia (urgent admission for CURB-65 score of 3-5)
  - cases with CURB-65 score of 2 (and potentially for a score of 1)
  - progressive development of influenza-related complications
  - bilateral pulmonary crackles or infiltrates on X-ray
  - worsening of pre-existing PID condition, however manifest

E2 Treatment of Children with PID

Recommendations (specific treatment measures in a non-inpatient setting):

- Cough and mild fever: treatment at home with antipyretics (not aspirin), fluids and rest (with low threshold for seeking help and advice).

- High fever (>38.5^{o}C) + cough or ILI:
  - oseltamivir: <1 year: unlicensed (but use may be justified in severely ill infants)

<15 kg: 30 mg b.d. (5 days)
15-23 kg: 45 mg b.d (5 days).
>24 kg: adult dosage, 75 mg b.d. (5 days)

- antibiotic: Offer antibiotic in all cases, combined with oseltamivir (>1 year).
  <12 years - co-amoxiclav or, if allergic, clarithromycin or cefuroxime
  >12 years - co-amoxiclav or doxycycline

- Indicators for hospital admission:
  - Signs of respiratory distress
  - Cyanosis
  - Severe dehydration
  - Altered conscious level
  - Complicated or prolonged seizure
  - Signs of septicaemia (extreme pallor, hypotension, floppy infant)

APPENDIX 1

Recommendations to increase basic personal awareness and optimise personal hygiene measures

(adapted from Department of Health draft Pandemic Influenza National Framework, March 2007)

Aims are to:

1) Decrease risks of becoming infected
2) Decrease risks of passing infection on to others
3) Interrupt transmission of infection via face, hands and fomites

- Appropriate isolation, voluntary quarantine and social distancing
- Where possible, avoiding contact with infected family members and social contacts
- Avoiding crowded gatherings where possible, especially in enclosed spaces
- Covering the nose and mouth with a tissue when coughing or sneezing
- Disposing of dirty tissues promptly and carefully (bag and bin)
- Frequent handwashing, especially after coughing/sneezing and disposing of tissues
- Ensuring children are aware of the need for enhanced simple personal hygiene measures
- Cleaning hard domestic surfaces (e.g. kitchen worktops, door handles, other potential fomites) frequently with normal cleaning products
- Wearing a disposable face mask when symptomatic and it is essential to go out, to protect others

APPENDIX 2

CURB-65 Score

Score 1 point for each feature present:

- **C**onfusion (mental test score of <8, or new disorientation in person, place or time)
- **U**rea >7 mmol/l
- **R**espiratory are >30/min
- **B**lood pressure (SBP <90 mmHg or DBP <60 mmHg)
- Age >**65** years

The CURB-65 score may be used to assess risk status of patients with pneumonia. **This tool has not been validated for use in the context of PID.**

- patients with a CURB-65 score of 3,4 or 5 are at high risk of death and should be managed as having severe pneumonia. Patients with bilateral lung infiltrates on chest radiography (consistent with primary viral pneumonia) should be managed as having severe pneumonia regardless of CURB-65 score.

- patients with a CURB-65 score of 2 are at increased risk of death and should be considered for short-stay inpatient treatment or hospital supervised outpatient treatment.

- patients with a CURB-65 score of 0 or 1 are at low risk of death, can be treated as having non-severe pneumonia and may be suitable for home treatment

The risks / benefits of hospital admission with low CURB-65 scores may need careful assessment, and re-assessment, in any pandemic situation.