Clinical Expert Statement Template

Thank you for agreeing to give us a personal statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them. Your statement can be as brief as you like, but we suggest a maximum of 8 pages.

If there are special reasons for exceeding this 8-page limit please attach an Executive Summary to your statement.

Re: Amantadine, oseltamivir and zanamivir for the treatment of influenza

Statement of personal experience:

I am a Consultant Chest Physician working in a large teaching hospital – Nottingham University Hospitals, City Hospital Campus. I have a specific interest in respiratory infections and am currently Chair of the British Thoracic Society's Respiratory Infection Specialist Advisory Group and Chair of the British Thoracic Society's Community Acquired Pneumonia Guidelines Committee. I was Chair of the joint British Thoracic Society, British Infection Society, HPA and DoH Pandemic Influenza Clinical Management Guidelines Committee.

Given that my experience is mainly in hospital practice, I have limited most of my comments to the use of antivirals (taken here to refer to amantadine, oseltamivir and zanamivir) in hospital.

What is the place of the technology in current practice?

How is the condition currently treated in the NHS?

Influenza presents mainly as an acute respiratory infection with symptoms of an influenza-like illness (ILI), particularly cough and fever. Uncomplicated influenza is a self-limiting illness. Treatment is supportive and generally occurs in the community. Antivirals are occasionally used in accordance to NICE guidelines 2003.

The main reasons for hospitalisation of patients with influenza include:(a) the development of pneumonia as a complication - this is usually a secondary pneumonia caused by bacterial pathogens; (b) social needs consequent on uncomplicated influenza – particularly affecting the elderly; (c) instability of co-morbid illnesses consequent on influenza infection, such as exacerbation of chronic obstructive airways disease (COPD) or worsening cardiac failure.

Treatment in hospital is mainly directed at the resulting complication or unstable co-morbid illness. Antivirals are rarely used in hospitals in the UK in the management of these patients.

For instance: Nottingham University Hospitals (NUH) Trust provides acute medical care for a catchment population of approximately 650,000 patients. At NUH, oseltamivir is the antiviral of choice for influenza-related infection. In a 12 month period (April 2007 to March 2008), 98 courses of oseltamivir tablets (75mg bd for 5 days) were prescribed of which only 2 courses were prescribed from the Medical Admissions unit and 8 courses from the Respiratory wards. (The remainder of the antiviral courses were prescribed from Haematology (70 courses), Oncology (12 courses), Infectious Diseases (2 courses) and Adult Critical Care (4 courses) wards and the likely reason for the higher use of antivirals in these areas is covered later.) These figures reflect the experience of clinicians in other hospitals including London, Edinburgh and Manchester areas. {personal communications}

The lack of use of antivirals in hospitals is partly because patients usually present to hospital >48 hours after symptom onset and the diagnosis of influenza infection is not usually confirmed expediently. In addition, evidence supporting the value of antivirals in patients presenting to hospital is weak.

Is there significant geographical variation in current practice?

Specific figures have not been compared. Nevertheless, no significant geographical variation in the hospital use of antivirals is expected in the UK.

Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There are currently no good alternatives to the antivirals being considered.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients who are immunocompromised and have influenza infection have a worse prognosis compared to immunocompetent patients; in particular, they suffer higher rates of respiratory related complications such as pneumonia. Immunocompromised patients also have higher levels and more a prolonged period of viral shedding compared to immunocompetent patients. {Nichol WG et al, Clin Infect Dis 2004;39:1300 – 1306} Such patients may benefit from the use of antivirals outside the current NICE 2003 recommendations (ie. beyond 48 hours from symptom onset, or outside the assigned period when influenza is circulating). This belief of potential benefit is reflected in the greater use of antivirals in patients with haematological and oncological illnesses; these patients generally having the highest degree of immunocompromise amongst hospitalised patients. (see earlier figures of oseltamivir use at NUH – 70 of 98 courses used in Haematology wards - note: the Haematology department at NUH is a regional centre with expertise in bone marrow transplant) Unfortunately, there is a paucity of robust data to support such use. In addition, the potential persistence of viral shedding whilst on antiviral therapy raises concerns regarding the development of antiviral resistance.

Similarly, whether patients who are severely ill from influenza-related pneumonia benefit from antiviral use outside the current NICE 2003 recommendations is unknown. Almost all the data on antivirals relate to patients with uncomplicated influenza.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Antivirals should be available in primary and secondary care.

The value of antivirals for the treatment of influenza in long-term care facilities could be considered a special situation as outbreaks within these institutions are well-recognised and these outbreaks may occur outside the period 'when influenza is circulating'. If influenza is confirmed to be circulating *within* such an institution, there are good reasons to consider the use of antivirals (for treatment) regardless of rates of influenza in the wider community. This would currently fall outside the NICE 2003 recommendations. The use of antivirals in these circumstances may require additional professional advice from the HPA.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The 2007 Infectious Diseases Society of American(IDSA)/ American Thoracic Society (ATS) Consensus Guidelines on the Management of Community-Acquired Pneumonia states: " Use of oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for >48 h (level I evidence), but these drugs may be used to reduce viral shedding in hospitalised patients or for influenza pneumonia. (Moderate recommendation; level III evidence)" The methodology for this Guideline is considered robust

and a full description is given in the Guideline document. {Mandell LA et al. Clin Infect Dis 2007:44:S27 – 72}

The 2005 European Respiratory Society Guidelines for the Management of Lower Respiratory Tract Infections recommends that "Only in high-risk patients who have typical influenza symptoms, for <2 days, and during a known influenza epidemic, can anti-viral treatment be considered. (C1)" {Woodhead M et al, ERJ 2005;26:1138 – 1180} Grading methodology is detailed in the Guideline.

The British Thoracic Society (BTS) Guidelines for the Management of Community Acquired Pneumonia is being updated (expected publication in 2009). The current BTS Guidelines do not specifically mention antiviral use.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology in clinical practice reflects that observed under clinical trial conditions. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

What, in your view, are the most important outcomes and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK.
Is the technology easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

In the need to administer antivirals early (within 2 days of symptom onset) in order to obtain maximum clinical benefit is one of the major limitations of this treatment particularly in hospital practice where patients tend to present later in their illness.

Linked to this is the issue of establishing an early diagnosis of influenza .

In a retrospective cohort study of adults with influenza admitted to Prince of Wales Hospital, Hong Kong between 1 January 2004 and 31 December 2005, the use of oseltamivir within 48 hours of symptom onset was associated with a reduced length of stay (median 4 days compared to 6 days, adjusted hazard ratio 1.54, 95%CI 1.23 – 1.92). {Lee N et al. Antiviral Therapy 2007;12:501 -508} No reduction in LOS was observed in patients who received oseltamivir > 2 days from symptom onset. At that hospital, following the SARS outbreak, all adults presenting with fever, respiratory and systemic symptoms had a nasopharyngeal aspirate sample tested using an influenza-specific immunofluorescence assay. Results were available to clinicians within hours of testing.

The widespread use of rapid influenza diagnostic tests to guide antiviral treatment is not established. Instead, antiviral use is mainly empirical, based on a symptom complex and limited to periods of influenza activity. Whilst this strategy is relevant for most healthy individuals presenting in the community, it is less clear how applicable it is to patients with co-morbid illnesses presenting to hospital/ in hospital.

For instance, in a prospective observational study of patients presenting to an emergency department during a period of influenza activity, of those with subsequently confirmed influenza infection, only 40% had a classic ILI. {Monmany J et al, Infection 2004;32:89-97}

Similarly, in a retrospective case series of 207 hospitalised patients with a diagnosis of influenza virus infection over 3 influenza seasons, criteria for an ILI was observed in only 51%. {Babcock HM et al. Infect Control Hosp Epidemiol 2006;27:266 – 270}

Conversely, in patients with COPD, 10 – 25% of exacerbations may be due to influenza virus infection. These patients are likely to stand to gain from the early use of antivirals. However, exacerbations due to rhinovirus and respiratory syncytial virus infections occur with equal or greater frequency and are clinically indistinguishable. Regardless of viral pathogen, most exacerbations occur over the winter months. Therefore, it is difficult to establish a diagnosis of influenza-related exacerbation of COPD based on symptoms of an ILI alone, whether in the community or in hospital, especially outside periods of peak influenza activity.

Summary of opinion

1. Antivirals are rarely used in the hospital setting currently.

2. Consideration should be given to the use of antivirals in the following circumstances:
a) severe influenza-related pneumonia regardless of immune status
b) beyond 48 hours in immunocompromised patients with influenza virus infection.
It is acknowledged that while there is no good evidence of benefit in the use of antivirals in these circumstances, neither is there evidence of harm or lack of benefit. Clinically, the potential for benefit as opposed to harm in these circumstances is arguably in favour of antiviral use.

3. Antiviral use within institutions (long-term care facilities and hospitals) should not be restricted to periods of high influenza activity in the community (based on RCGP consultation rates).

4. There should be further research into the use of antivirals in hospitalised patients, including patients who do not present with the classic symptoms of an influenza-like illness.

5. The value of near patient testing for influenza virus infection in order to guide antiviral use in selected patient groups warrants consideration.

6. Experience in the use of antivirals in hospitals for seasonal influenza will inform the use of antivirals during a pandemic. The value of this experience is difficult to quantify, but should not be underestimated.

Dr Wei Shen Lim
27 June 2008

Any additional sources of evidence?

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Please note: The NHS is required by the Department of Health and Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.
If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and Welsh Assembly Government to vary this direction.
Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

Should there be a broadening of the NICE recommendation on the use of antivirals which includes the selected use of rapid influenza diagnostic testing in hospital, then additional training and education of NHS staff (eg. how to take a nasopharyngeal sample) and additional resources (eg. diagnostic facilities/ kits) may be required.