

Briefing and guidance for adult renal units in the UK during an influenza pandemic

Prepared by the Renal Association Clinical Affairs Board / JSC Renal Medicine

24.10.07

1. Introduction

This guidance document has been produced for adult renal units in the UK, to help in their preparation and planning for a possible future influenza pandemic. It summarises key background aspects to such a pandemic, and detailed consideration as to how the vital aspects of the renal service can be maintained and non-essential work curtailed, during the huge challenges to the safe and effective delivery of health care that will result.

Many of the issues that hospital specialties have to consider are generic, and there are already important Department of Health documents produced (and being constantly updated) as guidance for the health service in general, and acute hospital trusts in particular. The relevant content from these documents has been included in this specialty-specific guidance.

SHAs and PCTs, all of whom will be individually responsible in their areas for the command and control structures and management of the pandemic, have or should be in the process of developing their local policies. Similarly hospital trusts should be developing their own policies that integrate and cross-reference to other local and national policies.

Thus whilst this guidance document highlights issues relevant to renal services, this must be read in the context of local policies. The Department of Health home page for an influenza pandemic is <http://www.dh.gov.uk/en/PandemicFlu/index.htm>, with DH documents relevant to this paper found at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_073185.

2. Influenza pandemic: key background

Influenza pandemics occur at variable frequency. During the last century, they occurred in 1918/19 ('Spanish Flu'), 1957 ('Asian Flu'), the most recent in 1968 ('Hong Kong Flu'). The longest interval known between these pandemics was that from 1918-1957, i.e. 39 years. It is considered inevitable that there will be another pandemic in the future, but there is no way to predict exactly when.

Whilst any new strain of the influenza virus could trigger a pandemic, current concerns include the possibility that a mutation of the avian H5/N1 influenza virus will allow it to readily infect and be transmitted by humans. Usually 5-15% of the population become clinically infected with influenza, but in a pandemic this is likely to be 25-50%. The planning assumption for the UK is that up to 4% of symptomatic patients would warrant hospital admission (if capacity were available). UK mortality in previous pandemics has been 0.2-2.0% of those with symptoms. Current national planning assumes a case fatality rate of 0.4-2.5% of those with symptoms. This translates to a best case UK mortality of 55,500 and worst case of 750,000.

Substantial preparations are being made nationally and internationally to plan the response for a pandemic. In the UK the Department of Health and the NHS will of course play a key (but by no means exclusive) role. There will be huge challenges for all aspects of health care delivery both in hospitals and primary care, and a radical re-prioritisation of healthcare delivery will be required to ensure life saving treatment can be provided to all patients in need of it, at the expense of less urgent clinical care, which will need to be curtailed until the effects of the pandemic settle.

The predicted progression of a pandemic across the world and in the UK is summarised in the following WHO and UK phases and alert levels.

WHO international phases and UK alert levels for an influenza pandemic

WHO international phases		UK Impact
Inter-pandemic period		
1	No new influenza virus subtypes detected in humans	UK not affected unless it has strong travel and trade connections with affected country
2	Animal influenza virus subtype poses substantial risk	
Pandemic alert period		
3	Human infection(s) with a new subtype, but no (or rare) person-to-person spread to a close contact	UK not affected unless infection starts in the UK or it has strong travel and trade connections with affected country
4	Small cluster(s) with limited person-to-person transmission but spread is highly localised, suggesting that the virus is not well adapted to humans	
5	Large cluster(s) but person-to-person spread still localised, suggesting that the virus is becoming increasingly better adapted to humans	
Pandemic period		
6	Increased and sustained transmission in general population	UK alert levels 1 Virus/cases only outside the UK 2 Virus isolated in the UK 3 Outbreak(s) in the UK 4 Widespread activity across the UK

Modelling suggests that during an influenza pandemic there will be peaks in demand which may overwhelm capacity, including capacity for specialised treatments or limited resources such as critical care. Under these circumstances it will be impossible for trusts to provide the usual standards of medical care. Available resources will therefore limit the standard of care that can be provided in the emergency, and decisions will need to be made on how to provide care that is ethically and clinically appropriate.

Although normal services will need to be sustained as long as possible, there will come a point when a fundamental shift in the pattern of care provision will be required to prioritise the needs of large numbers of infected patients together with non-infected patients with urgent clinical needs. At WHO Phase 6, UK alert level 2, activities may need to be scaled back in anticipation of a rapid surge in influenza cases in the UK. At WHO Phase 6, UK alert levels 3 and 4 (where there are outbreaks and epidemics or widespread influenza activity in the country), it is anticipated that even life-saving activities will be difficult to sustain, so non-essential activities will have to be discontinued. Thus, at the earlier stages of the pandemic, it will be appropriate to cease some routine surgery and outpatient services. At later phases of an influenza pandemic where there is widespread disease, it may be necessary to cancel **all** elective clinical functions and concentrate on expanding capacity for management of influenza and non-influenza emergency cases.

Local response plans should focus primarily on ways of supplementing and making the most effective use of the staffing and beds, with particular attention given to facilitating rapid discharge arrangements. Alternative care sites may need to be set up, such as private hospital/clinic facilities.

Pandemics often have second or third waves, occurring up to some months after the first wave. These can be as severe and disruptive, or more so, than the first wave, and planning needs to take this possible eventuality into account.

3. Renal-specific aspects of a pandemic

a) Specific risks to renal patients of influenza infection and its complications

In conventional influenza infection, patients at increased risk of complications are considered to be: those aged 65 years or older; long stay residential care home residents; and those with: chronic respiratory diseases; chronic heart disease; chronic kidney disease, nephrotic syndrome and established renal failure; chronic liver disease; diabetes, and immuno-compromised patients. It should be noted that for kidney patients, it is hard to find good published evidence that renal patients are indeed at such increased risk.

The particular complications associated with high morbidity and mortality are influenza pneumonitis and secondary bacterial pneumonia caused by *Streptococcus pneumoniae* or *Haemophilus influenzae*, or sometimes *Staphylococcus aureus* or other healthcare-associated organisms.

Influenza virus infection has also been associated with worsening in the clinical condition of patients with a range of existing medical conditions, such as heart failure, diabetes, coronary heart disease, asthma and chronic obstructive pulmonary disease (COPD).

Finally, patients with pre-existing CKD are at risk of pre-renal exacerbation through pyrexia, poor fluid intake from anorexia and sore throat, diarrhoea (which has been reported in a high proportion of avian flu sufferers), and NSAIDs used by patients for treatment of myalgias and headaches.

Thus renal patients, many of whom have the above listed comorbidities or risk factors, are likely to be more at risk of serious morbidity and mortality during a pandemic. This will result in additional and perhaps disproportionate pressure on renal units where the skills for caring for these patients are concentrated.

b) Staffing issues

Up to 50% of the workforce may require time off work at some stage over the entire period of the pandemic. Staff absence from work will be not just due to personal influenza infection, but also to provide care for dependants (whether ill relatives, or children as a result of likely school closures), family bereavement, other psychosocial impacts, fear of infection and/or practical difficulties in getting to work. At the peak of the pandemic, between 15% and 20% of staff may be absent at any one time.

All hospital doctors, whatever their base specialty, are likely to be involved in the care of patients with influenza. Nephrologists (because they have general skills) will need to be prepared to help out in other clinical areas where possible.

As all elective in-patient and non-urgent out-patient activity will be cancelled during the pandemic, new working patterns and responsibilities will need to be brought in to place to cope with the demands of the acute in-patient workload.

Modelling suggests that small organisational units (5 to 15 staff) or small teams within larger organisational units are likely to suffer higher percentages of staff absences – up to 30–35% over a two- to three-week period at the local peak. This may have a significant impact on the running of satellite dialysis units.

Flexible (and extended) working rotas will be needed to cover staff shortages and emergency workload. An influenza pandemic will put staff under considerable pressure and there are likely to be conflicts between staff's professional and/or contractual obligations, personal or family responsibilities and concerns about risks. The Department of Health is working with NHS Employers to produce detailed guidance for human resource management during a pandemic. This guidance will have relevance to the ethical and professional obligations of staff.

There are potential legal issues that may impinge on Trusts' influenza pandemic plans. These range from regulatory matters through to concerns about staff undertaking unfamiliar roles, and Trusts/specialties temporarily providing levels of treatment which differ from those recommended in the usual protocols. The Department of Health again is currently in discussion with the stakeholders concerned on how these issues may be managed.

c) In-patients

Estimates suggest that existing hospital capacity may only meet 20% to 25% of the expected demand at the peak of the pandemic wave. Proportionate admission thresholds based on clinical management guidelines will therefore need to be agreed and progressively applied across specialties within trusts. Consistency and equity in the application of such thresholds will be an important factor in gaining public understanding and maintaining confidence. Common understanding and interpretation of those guidelines by health professionals at the primary, secondary and social care interfaces are particularly important.

Renal unit beds will be in great demand. Dialysis patients are more at risk of getting influenza infection and, when infected, of suffering a more severe clinical course. Unless they need ventilatory support, the inpatient care of such patients will need to be in an area where dialysis equipment and the appropriately trained staff are located. The tension between demands on the hospital trust to care for its local DGH population and of the renal unit to provide care for a wider catchment area will be significantly more acute than usual.

d) Haemodialysis

Challenges to the ongoing provision of maintenance out-patient haemodialysis for patients in established renal failure include:

- Staff shortages affecting the main unit and satellite units
- Difficulty cohorting infected patients when attending for dialysis
- Unavoidable exposure of staff to infected patients who need regular treatment
- Risks to hospital transport
- Risk to supplies and their delivery
- Carer illness implications for patients on home dialysis programmes
- Possible shortage of technicians

e) Peritoneal dialysis

Peritoneal dialysis patients have the relative advantage over unit-based haemodialysis patients of not needing to attend hospital regularly. This will reduce their exposure to infection. However the specific risks they face are:

- Uncertainty over delivery of PD supplies.
- Nursing and medical support
- Increased risk of infection through reduced immunity

It will also be difficult to maintain a service that can commence new patients on PD, mainly through a lack of nurses to provide the intensive training required..

f) Transplantation programs

It is unlikely that there will be the human and hospital resources during a severe pandemic for living or deceased donor kidney transplant programs to operate. Given the multiple personnel involved in successfully organising and seeing through a renal transplant, the pressures on the hospital facilities (particularly beds and critical care), and the enhanced risk of infection acquired in the peri-procedural period, it is possible that transplant programs will need to be temporarily suspended.

g) Out-patients

All non-urgent out-patient activity will need to be cancelled for a period that could be between two and five months, depending on the behaviour of the pandemic locally. The need to provide the emergency in-patient care for influenza and non-influenza cases will be overwhelming, and staff who are able to attend for work, and facilities, will be triaged to life-saving work on the wards.

However each specialty has a complement of patients under long term out-patient care who require ongoing careful supervision to avoid serious complications of their condition or its treatment. Some new referrals will still be necessary for those needing urgent out-patient assessment and management. The challenge will be to ensure the availability of such urgent care.

Trusts and individual specialties must be well prepared in advance so that they respond as soon as an impending pandemic is recognised. Systems should be in place to inform all patients under the care of specialist services, with advice on how to seek help by telephone or other means, and of changes in arrangements of outpatient attendance and inpatient procedures.

The Department of Health is developing guidance on the management of outpatient cases during an influenza pandemic and is due to issue further details in due course.

4. Recommendations for renal unit planning

a) General measures

- Register all contact details (including mobile phone numbers, and email addresses where available), for all dialysis, transplant, other immunosuppressed and low clearance patients, to ensure failsafe communication lines, and enhance the potential for virtual or distant disease management.
- Prevent cross infection in renal unit areas through segregation and cohorting of influenza patients in clinical areas. Such cohorting will be required whenever possible on wards, haemodialysis units, and in out-patient areas. Units will need to consider how they can achieve this within the constraints of their unit's design and flexibility.
- Follow local and national guidance on the prevention of spread of infection through protective clothing, masks, barrier nursing etc.
- Be prepared to have other parts of the renal unit adapted for inpatient activity if feasible.
- Identify key supplies, and ensure supply lines maintained. This is particularly the case for renal unit haemodialysis supplies. It is assumed that peritoneal and haemodialysis (hospital and home) suppliers will have contingency plans in place for a pandemic, but it is advised that renal units check that these are in place with their suppliers.
- Guidance on the clinical management of patients with influenza-like symptoms during a pandemic is available at www.brit-thoracic.org.uk/PandemicFlu.html. This will almost certainly be updated as more is learnt of the nature and behavior of the influenza virus causing the pandemic.

b) In-patients

- Treatment and admission criteria should be transparent and applied in a consistent and equitable way, utilising available capacity for the most seriously ill. Such criteria are likely to be developed nationally or on an SHA basis, but specialist medical staff will probably need to contribute to daily triage and management decisions in any period when the demand for emergency beds exceeds the supply.
- Mechanisms for rapid discharge and follow up where necessary should be established.
- Staff should be prepared to acquire additional skills at short notice for helping with the care of critically ill patients, many with acute respiratory failure, as intensive care units will be overwhelmed. Such additional training might include the administration of non-invasive ventilation.
- There will be an expectation that all elective admissions will need to be cancelled. Renal units will need to decide which non-emergency admissions they consider are still essential to prevent significant subsequent morbidity.

- Routine renal admissions that would need to be cancelled/postponed until the pandemic had subsided include:
 - Renal biopsies, unless a) rapidly deteriorating renal function with no other apparent cause, or b) nephrotic syndrome. It may prove exceptionally difficult to admit patients even with these presentations, and such patients may need to be treated 'blind' based on the balance of clinical probabilities
 - Renal artery stenting unless known tight stenosis in a single kidney/bilateral critical renal artery stenosis with deteriorating function
 - Vascular access surgery, unless critical shortage of central veins for a catheter. Whether cancelling such surgery is necessary will depend on the local pressures on the trust's beds and staff, and individual cases based on the clinical urgency. It may be that day case surgery for AV fistula creation could keep going if the facility and surgical staff are available (which is likely, as most other routine surgical work is going to be cancelled). Surgery requiring in-patient management is very likely to be cancelled unless clinically urgent
 - Renal transplant surgery (see above)
 - Coronary angiography for transplant work up
 - Parathyroidectomy unless severe hypercalcaemia unresponsive to medical treatment

c) Haemodialysis

- Consider selecting suitable patients for twice weekly treatment, in the event that staffing levels in dialysis units can not support three times weekly haemodialysis for all. Individual units will need to assess the safety of such an approach, in part determined by knowledge of residual renal function.
- Consider setting up or expanding night shifts for haemodialysis in the main hospital unit. As a result of a) reduced staffing levels in satellite units, and b) influenza infection of home haemodialysis patients or their carers, there is likely to be a significant increase in patients needing to receive haemodialysis in the main hospital unit.
- Cohort infected/uninfected patients separately wherever possible on the dialysis unit
- Refresher/induction courses for renal nurses not experienced in haemodialysis may be required to ensure there are enough such nurses to provide haemodialysis in main units/satellites
- Cancel routine out-patient visits
- Consider asking home dialysis patients and their carers to provide dialysis for non-infected hospital patients

d) Peritoneal Dialysis

- Ensure with suppliers that there are contingency plans in place to ensure delivery of PD fluids to patients' homes
- Patients may benefit from stockpiling fluids where possible (to be discussed with suppliers)
- Cancel routine out-patient appointments, but arrange for essential blood tests to be done, locally wherever possible

e) Outpatients

- It should be assumed that all previously arranged outpatient clinics will be cancelled by the time UK alert level 3 is reached, and Choose and Book will be suspended. New emergency clinics will need to be established, to see only those patients who genuinely need to attend the hospital for specialist review as opposed to distance/virtual/primary care management.
- Stable general nephrology, transplant, dialysis and low clearance patients should be managed by remote blood test monitoring (when required) without needing a hospital visit. A lower frequency of blood testing may need to be accepted if phlebotomy services are compromised.
- Each renal unit will need to decide which criteria to use for determining the patients who genuinely need to be seen, but these criteria should be strict and centre on preventing or treating rapid progression of their underlying renal disease, and avoiding life-threatening complications of treatment (particularly recently commenced immunosuppressive regimens).
- Suggested categories of patients warranting hospital out-patient review are:
 - New referrals with nephrotic syndrome, rapidly worsening renal impairment, acute multi-system disease with renal involvement, severe hypertension (if nephrology provides this service in the trust)
 - Specialist long term renal patients (transplant, low clearance, other immuno-suppressed, dialysis) who are acutely unwell, following a telephone consultation
- An effective emergency administrative structure will need to be set up in renal units. This is required for a) effective communication with patients during the pandemic, and b) to provide effective virtual clinical management. Considerations include:
 - Setting up patient email address and mobile and home phone lists for efficient communication of general and personal advice and instructions
 - Setting up dedicated departmental emergency phone lines and email addresses for patients to access the renal department directly. Trusts with effective web sites could be rapidly adapted to direct patients to the appropriate pages for their condition(s)
 - Establishing rotas for medical, nursing and clerical staff to man the virtual clinics, review results and liaise with patients

Appendix

Oseltamivir (Tamiflu) dosing in patients with reduced renal function

Oseltamivir reduces the severity and duration of symptoms of influenza if taken within 48 hours of the commencement of symptoms. In the early phases of the pandemic it is expected that all such patients will be offered oseltamivir, but as the pandemic develops it is unclear what criteria will be used for prescription, particularly if demand exceeds supply. It is expected that the prescription of oseltamivir for outpatients will be managed by PCTs and primary care staff.

As discussed earlier, renal patients are a group at high risk of adverse outcomes from influenza infection, and are likely to benefit at least as much as other patient groups from such therapy. However clarification is needed on dosing in renal patients. Tamiflu is not licenced for use in patients with severe renal impairment or on dialysis, and the Roche UK SPC for Tamiflu recommends halving of the dose if the creatinine clearance is 11-30, and avoiding it all together if the CrCl is <10ml/min or the patient is on dialysis. This would therefore exclude such high risk patients from the potential benefits of the drug during a pandemic.

Pharmacokinetics of oseltamivir

Tamiflu is oseltamivir phosphate, which is a pro-drug which is well absorbed, and converted to the active metabolite oseltamivir carboxylate by predominantly hepatic esterases. The volume of distribution is 23 litres equates to extracellular fluid volume. Plasma protein binding is negligible (3%). The active metabolite oseltamivir carboxylate is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration.

Effect of renal impairment on pharmacokinetics

Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function.

The only significant study in the literature on the pharmacokinetics of oseltamivir (suspension) in peritoneal and haemodialysis patients is Robson R et al; NDT 2006; 21:2556-62. [<http://ndt.oxfordjournals.org/cgi/content/abstract/21/9/2556> for abstract]. They investigated 30 mg dosing with oseltamivir suspension, and their data is incorporated into the US Tamiflu Product Information (Nov 2006) <http://www.rocheusa.com/products/tamiflu/pi.pdf> as follows:

Oseltamivir carboxylate exposures in patients with normal and reduced serum creatinine clearance.

Parameter	Normal Renal Function			Impaired Renal Function				
	75 mg qd	75 mg bid	150 mg bid	Creatinine Clearance <10 mL/min		Creatinine Clearance >10 and < 30 mL/min		
				CAPD	Hemodialysis	75 mg daily	75 mg alternate days	30 mg daily
				30 mg weekly**	30 mg alternate HD cycle			
C_{max}	259*	348*	705*	766	850	1638	1175	655
C_{min}	39*	138*	288*	62	48	864	209	346
AUC₄₈	7476*	10876*	21864*	17381	12429	62636	21999	25054

*Observed values. All other values are predicted.

AUC normalized to 48 hours

**The 30 mg dose can be provided by using the oseltamivir suspension

On this basis, it seems appropriate to consider prophylaxis or treatment of patients with renal impairment with oseltamivir as follows:

Proposed Renal Association oseltamivir dosing recommendations for patients with reduced renal function (approved by UK Renal Pharmacist Group)

Creatinine clearance	Recommended treatment dose	Recommended prophylactic dose
>30 ml/min	75 mg twice daily.	75 mg once daily
11-30 ml/min	75 mg once daily (or 30 mg suspension twice daily)	75 mg every second day (or 30 mg suspension once daily)
Haemodialysis patients	30 mg suspension after alternate haemodialysis sessions	30 mg suspension, single dose (given post-dialysis where possible)*
Peritoneal dialysis patients	30 mg suspension weekly	30 mg suspension, single dose*
≤ 10 ml/min (not on dialysis)	30 mg every 10 days **	30 mg suspension, single dose*

*Single dose recommendation based on recommended duration of course of 5 days in patients with normal renal function.

** Based on reported contribution of excretion from PD of 36% in Robson et al NDT 2006.

Interaction with other medications relevant to renal patients

In-vitro studies demonstrated, that neither oseltamivir, nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. i.e. unlikely to affect CsA/tac levels.