THE RENAL ASSOCIATION

Treatment of adult patients with renal failure

Recommended standards and audit measures

SECOND EDITION

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RENAL ASSOCIATION and the ROYAL COLLEGE OF PHYSICIANS OF LONDON
in collaboration with the BRITISH TRANSPLANTATION SOCIETY
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Foreword

In April 1995 the Renal Association and the Royal College of Physicians produced a standards document for clinical nephrology, *Treatment of adult patients with renal failure*, which provided guidelines to both providers and purchasers of renal services. Why then should a second edition be published so soon?

Renal medicine is a high-cost, low-volume specialty and is, like many other specialties, under scrutiny to provide cost-effective treatment for its patients. Within the past three years there has been increasing interest in evidence based medicine and it is clear that renal medicine should take advantage of the databases that have been created, including the Cochrane collaboration. Consequently, the increase in information from these sources has significantly increased the size of the standards document, such that it has now become a 'mini textbook' of nephrology which will be of great use to all individuals, clinical or non-clinical, involved in the care of patients with renal disease. In coping with the increasing workload associated with end stage renal failure such standards give, in the majority of cases, clear guidance regarding the parameters for many aspects of treatment. The scope of the document has also been widened, in collaboration with the Intensive Care Society and the British Transplantation Society, to include guidance for patients with acute renal failure and renal transplantation. The combined resources of the Renal Registry and the Audit Committee of the Renal Association will now be able to monitor the standards of care given to all patients with renal disease to enable comparisons to be made between units within the United Kingdom and with international standards.

The bulk of the work of compiling this document has been carried out and co-ordinated by Professor J Stewart Cameron, past President of the Renal Association, and we are very grateful to him and to all those involved in the production of the document, especially to the staff of the Royal College of Physicians Publication Unit, for completing this mammoth task. It is our intention that the document will have the widest possible circulation to inform all those involved in providing a renal service of which we can be justifiably proud.

November 1997

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1 Introduction

Background

1.1 In 1990 the Executive Committee of the Renal Association resolved to produce two policy documents on the treatment of adult patients with renal failure and charged two subcommittees with their preparation. The first document, *Provision of services for adult patients with renal disease in the United Kingdom* [Renal Association 1991], described the resources required.

1.2 This complementary document is the consensus statement of recommended standards and good practice for treatment of renal failure, revised and extended from its first edition [Renal Association 1995]. It was produced on behalf of the Executive Committee of the Renal Association and approved by the Renal Disease Committee and the Council of the Royal College of Physicians of London. For this new edition the collaboration of the British Transplantation Society was sought in composing the chapter on renal transplantation, and that of the Intensive Care Society for the chapter on acute renal failure.

1.3 The *Review of renal services in England* [Department of Health 1996a], published in May 1996 by the Health Care Strategy Unit of the National Health Service (NHS) Executive, gives in some detail the situation with regard to treatment of renal failure in England in 1993–4. In terms of global budget, on average about 1.4–1.6% of NHS revenue was spent on renal services, though the variation was great between purchasing authorities. The demographic data are being updated to 1996 at the time of writing.

1.4 The special needs of children with renal failure have not been included in the main text; they have been described in a report of a working party of the British Association for Paediatric Nephrology [1995], *The provision of services in the UK for children and adolescents with renal disease*, which should be read in conjunction with the current document; its salient features are summarised in Appendix 2.

Drafting of the document

1.5 The drafts of both editions of this document were circulated to all UK renal units in May 1993 (first edition) and July 1996 (this second edition). Many nephrologists commented in detail and we are grateful for their helpful input. The presidents of the European Dialysis and Transplant Nurses Association/European Renal Care Association, the Intensive Care Society, the British Transplantation Society and the renal dietitians group of the British Dietetic Association also received the document in draft, and it was revised in the light of the feedback received. We had to make some difficult decisions. These are discussed below together with the rationale for arriving at the conclusions reached.

■ ***The non-specialist reader is advised to read first Appendix 1, which is a review in non-technical language of the incidence, nature and treatment of renal disease.***

Defining the population

1.6 Standards and comparative audit will be meaningful only if applied to a well defined population of patients. The point at which a patient is deemed to have started renal replacement treatment is poorly defined, because of the variation in mode of presentation and time spent in resuscitation and deciding about suitability for long term treatment. A few patients who initially appear to be dialysis dependent recover sufficient renal function to survive without dialysis. Conversely, an increasing number of mainly elderly patients who appear initially to have acute, reversible renal failure do not recover renal function — 'acute irreversible renal failure' [Bhandari and Turney 1996; Firth 1996] (see Chapter 9).

1.7 In the United States of America, to overcome this problem, patients are regarded as having entered the programme 90 days following their transfer to a free-standing renal unit or 90 days following their first dialysis session. This ignores data from, and costs of, patients dying within the first 90 days of dialysis [Khan *et al* 1995; Soucie and McClellan 1996]. The recommendation of this report is to make assessments both from the time renal replacement therapy begins and from 90 days later.

Standards, targets and response to shortfall in practice

1.8 Standards can be set only for measurements that are reliable and comparable across the country. Unfortunately some measures highly desirable in practice, such as quality of life (see Chapter 12), are insufficiently standardised to permit this. In other areas (eg assessment of the quantity of dialysis delivered) techniques of measurement remain controversial and diverse (see 1.19, 1.20 and Appendix 4). However, standards can be set now for many categorical data such as plasma concentrations of important substances (eg immunoreactive parathormone (iPTH) or haemoglobin), numbers of adverse events occurring, expected levels of outcome success, or adherence to standard operational practice.

1.9 The mechanics of gathering and responding to data from patients requires some consideration. By the process of data collection, a *profile* of categorical measurements is obtained. This document and others similar to it, eg the Dialysis Outcomes Quality Initiative (DOQI) in the United States, add defined *targets* or *standards* [Will 1997] that these data should meet. How profiles may be expressed, and how standards and targets can be derived from them, is discussed further in Appendix 4.

1.10 Some standards may be set as *minima*; that is, all patients are expected to exceed this value, or a minimum target percentage of patients are expected to exceed the standard. Clearly the *mean/median* values for the group under treatment will be higher than these minima. Other targets will be set as *means*, eg patient or graft survival targets of patients taken on to end stage renal failure programmes. Other targets will consist of *rates*, eg complication rates in surgery, access surgery, or rates of primary success in creating A-V fistulas.

Shortfalls or inadequacies relative to standards

1.11 The nephrologist should respond to shortfalls or inadequacies in relation to defined standards according to the type of target and the degree of shortfall. Experience shows that in many areas of activity, such as complication and success rates of procedures, simply concentrating attention on the problem and the data

coming in leads to improvement, because the protocols that would be effective have not been carried out in practice, or no attention has been paid to available data, or no action taken as a result of examination of the data.

1.12 The response to shortfalls in relation to targets for categorical data, which form a profile with a range, mean or median, is more complicated. First, if there are obvious temporary reasons for the poor result in an individual (eg recent surgery or peritonitis) the result must be ignored and the assessment repeated later. More than one strategy is available when persistent shortfall is detected, but there are few data on what approach is most effective, in what situations each might be the optimal approach, and how long in each instance an improvement can be expected, beyond which 'failure' can be diagnosed.

(1) The first approach is to *transfer all patients on to a new 'improved' regimen*. Examples are to use longer dialysis sessions in the whole dialysis unit population to achieve better mean Kt/V (see Chapter 5), raise the bicarbonate concentration in the dialysate of all patients to eliminate acidosis, or assess blood pressure more frequently in every patient to achieve better control. This approach has disadvantages, in that patients who have already met the target do not need the alteration. The alteration may (and usually does) cost the provider more, with additional loss of opportunity costs in those who do not need it, and lays some patients open to possible side effects (eg if every dialysis patient were put on phosphate binders whatever their plasma phosphate concentration). Finally, unnecessary extra costs of time are imposed on patients who do not need the extra treatment (eg attending the clinic more frequently, or spending longer on dialysis).

(2) A second approach is to examine the profile and *concentrate only on those who have an apparent shortfall*. This is an extension of the usual medical practice of individualising treatment for each patient within accepted principles of therapy. These 'inadequately performing' patients are examined for the presence of known factors that could lead to their poor performance (eg poor blood flow in a haemodialysis (HD) patient, gastrointestinal blood loss accounting for persistent anaemia, non-compliance with treatment or peritoneal failure/loss of residual renal function in a patient on peritoneal dialysis). A typical example of this approach that is highly effective in practice is the use of erythropoietin to treat the anaemia of chronic renal failure. This approach implies also that following it will compress the range of values within the patient profile, which has not been demonstrated as yet, except in treatment of anaemia.

With either approach, repetitive assessment of all patients must be performed, since some patients who are initially on or beyond target may later fall below it, eg a patient on peritoneal dialysis whose residual renal function, and with it total creatinine clearance, declines.

It must be noted that patients appear as individuals in (2) above, but as members of a cohort in (1).

1.13 In practice, it seems likely that most units will use *both* techniques of improvement in performance, and initially profiles will be the result of retrospective analysis in unsorted patients treated with random strategies. In future they will be based on data collected prospectively from closely defined cohorts of patients treated in accordance with guidelines, which will permit more meaningful comparison between units and an assessment of what techniques are most appropriate in attaining what targets. Targets that may be applied to individuals need to be distinguished from interventions in groups of patients and targets to be set for the group. The introduction of new standards must trigger the audit cycle, testing the hypothesis that the new intervention will improve outcome, without increasing the side effects resulting from overtreatment.

1.14 The debate continues also whether to recommend minimum, average or optimal standards; we decided to define minimum and average standards, whilst prospective data collection should allow the setting of more exact and appropriate standards in the next edition of this document. Each time standards are raised, the benefit and the cost (including the extra costs of monitoring the new strategies) should be estimated. Unfortunately few cost effectiveness studies have been done in the field of renal medicine. We recognise that the early recommendations in this document and its predecessor will be refined in the light of the results of research and audit. A major contribution to both has been the establishment in 1996–7 of a National Renal Registry in Bristol which will collate patient data nationally. Already long term data from the United Kingdom Transplant Service Special Authority (UKTSSA) are available for renal transplantation.

Comorbidity scoring

1.15 Survival and rehabilitation are heavily influenced by factors such as age, race and medical comorbidity, that is other significant disease besides renal problems (see Appendix 4). For purposes of standard setting and comparative audit, patients should be grouped according to these characteristics. At the moment we have data only on the case-mix of patients being admitted currently to renal units in the United Kingdom, and *the standards recommended in this document should be taken to apply only to low and medium risk patients*, as defined in Appendix 4 (A4.7). Studies in progress to evaluate the prognostic importance of concurrent illnesses will allow us, in future documents, to ascribe a risk score to each patient [Khan *et al* 1995]. Since this information is not yet available, we have taken account only of age and diabetes, for which data are available, in keeping with the *Review of renal services in England*.

Protocols

1.16 Within each renal unit, after discussion, an agreed system of written protocols should be developed for all procedures, upon which practice in the unit should be based. Whilst deviations from the protocols will be necessary on occasion, they will ensure, apart from their educational value, a consistent standard of delivery of care. These protocols should be under regular review by medical, nursing and other staff.

Strength of supporting evidence

1.17 The strength of the evidence that adherence to a minimum standard will benefit patients is variable and in many areas low (B to C in the grading of the US Department of Health and Human Services [1992]*). The few controlled trials that have been done are identified as such in the reference list (**CT**); reviews (identified by **Review**), often not strictly peer reviewed, are marked also to indicate the strength of the evidence. In some cases no firm evidence is available, and interpretation must be circumspect.

■ ***The recommendations in this document are therefore titled:***

'**Recommended standard**' if the available evidence is strong;

'**Recommendation**' if it is weaker or speculative.

Some recommendations address organisational or ethical issues and have not been allocated evidence related grades.

1.18 In some areas we have not been able to make recommendations because data or even methodology upon which to base these are not yet available. However, we have identified these areas; audit should supply data for them within a reasonable period of time. It must be remembered that audit is not a substitute for controlled trials but an indication of what interventions should be investigated by trials. In a few areas (such as quality-of-life analysis), how best to measure outcomes is not yet established, and no recommendations can be made, or audit undertaken.

Standardisation of methodology

1.19 Standardisation of methods is necessary for standard setting and audit. Specific areas of concern and controversy in dialysis were: the amount of dialysis prescribed and/or delivered (especially in peritoneal dialysis); urea kinetic modelling; use of bicarbonate HD; twice weekly HD; measurement of serum albumin concentration; water standards; methods of expressing mortality rates. These have been addressed in this document, particularly in Appendix 4 which deals with methodology.

Presentation of data

1.20 We agreed that continuous data should be presented where possible as *cumulative frequency curves* to illustrate the distribution of the outcome variable in the patient population. This is well suited to demonstrating quality of care given and for comparing outcomes from different units. Again this method is discussed in Appendix 4, with examples.

*** Strength of recommendation:**

A = Evidence from at least one properly performed randomised controlled trial (quality of evidence Ib) or meta-analysis of several controlled trials (quality of evidence Ia).

B = Well conducted clinical studies, but no randomised clinical trials; evidence may be extensive but essentially descriptive (evidence levels IIa, IIb, III).

C = Evidence (level IV) obtained from expert committee reports or opinions, and/or clinical experience of respected authorities. This grading indicates an absence of directly applicable studies of good quality.

Service delivery

1.21 One of the determinants of quality of services for renal disease is the mode of delivery. However, in the absence of clear evidence of the optimum arrangements, we do not prescribe the means of delivering care. This topic is dealt with in detail in the previous publication of the Renal Association [1991] on the provision of renal services. However, it is worth mentioning here that progressively the care of patients in renal failure in the United Kingdom is shifting away from often large centralised units to generally smaller local units based in district general hospitals, either as independent entities or as satellite units served centrally.

Workload

1.22 Several renal centres remain concerned about the workload that would be involved in documenting compliance with standards and recommendations. We judged that this problem would have to be resolved, alongside many others, by negotiating with purchasing authorities the resources required to collect the necessary data.

Prices and costs

1.23 The implementation of these higher standards will have, in almost every case, cost implications which will need to be agreed with purchasing authorities. Prices and costs are mentioned only occasionally in this document. The *Review of renal services in England* recommends a template that can be used nationally to derive costs in a standard fashion, which will allow valid comparisons. Few studies on cost effectiveness of treatment have been done in renal medicine, and we hope these will be added to in the near future.

Future editions of this document and related output

1.24 This document is in a continuing series that the Renal Association plans to publish in association with the Royal College of Physicians. We intend to work further with purchasers to translate the service specification set out in this report into a model contract for the delivery of acute and chronic renal care. We aim to develop more detailed audit protocols, based upon the audit measures discussed in the various chapters and summarised in Appendix 3, to monitor the quality of care given in a whole renal service or to an individual patient. Both of these initiatives will be preceded by consultation with patients suffering from kidney disease and relevant health professionals. We aim also to undertake systematic literature reviews to complement the expanding database, which should permit revision of standards at an appropriate level and direction.

Throughout this document 'we' (think/recommend etc) means 'the Renal Association and the Royal College of Physicians of London', and implies acknowledgement of the views of the other bodies consulted.

2 Remit and purpose of this document

Renal failure in the context of the NHS

2.1 As in other medical specialties, the pattern of provision of treatment for patients with renal disease is changing rapidly within the context of the 1990 NHS reforms. Whilst there are great opportunities to improve equity of access to renal services throughout the population, the costs per patient are high. The Renal Association recognises that developing the service cannot be solely provider led, and acknowledges its obligation to aid purchasers in making informed judgements. The document *Provision of services for adult patients with renal disease in the UK* [Renal Association 1991] detailed the resources and manpower that would be required to achieve a target end stage renal failure (ESRF) acceptance rate of 80 new patients per million population per year. It aimed to assist purchaser/provider negotiations and to enable costs to be calculated. The *Review of renal services in England* [Department of Health 1996a] incorporated data on provision locally and nationally throughout England, and provided a model for the purchasing of renal services. Finally, the document *The provision of services in the UK for children and adolescents with renal disease* [British Association for Paediatric Nephrology 1995] outlines the manpower implications for paediatric nephrology.

Purpose of this document

2.2 The purpose of this complementary document is to provide a framework of quality standards and guidelines on patient specific indicators that may be relevant in determining the well-being of, and outcomes in, patients with renal disease, in particular those with ESRF. It is hoped that this will allow contracts to be more focused and encourage providers to pursue comparative audit initiatives. The aim is to protect patients from the effects of substandard treatment and to improve the general quality of their care.

Aims

2.3 It is anticipated that this document will continue a process that will involve the regular review and revision of the standards set, and the introduction of further guidelines in new areas [Grimshaw and Russell 1993]. This second edition of the standards document deals in much more detail with acute renal failure, transplantation and chronic renal failure whilst still providing detailed consideration of treatments for ESRF.

Contents

2.4 This document considers:

- End stage renal failure (haemodialysis, peritoneal dialysis)
- Transplantation
- Acute renal failure
- Pre-dialysis chronic renal failure

- General nephrology
- Audit
- Methodology

The main text deals only with adult patients, defined as those over 18 years of age. Additional requirements for audit and treatment of children with renal disease are provided in Appendix 2.

3 End stage renal failure

Introduction

3.1 The end stage renal failure (ESRF) programme in the UK remains unbalanced. In the number of transplants performed and the results obtained it compares well with other countries, but the uptake of dialysis facilities, particularly for haemodialysis (HD), remains well below the desirable level [Department of Health 1996a]. Many hospital HD units are small and congested, and the UK remains heavily dependent on continuous ambulatory peritoneal dialysis (CAPD), a method of treatment with lower technique survival compared with HD [Gokal *et al* 1987; Maiorca *et al* 1991]. However, when corrected for case-mix, CAPD in general gives comparable patient survival to HD [Nolph 1996], but this point remains controversial.

3.2 In countries with a free choice of dialysis technique, such as in Scandinavia, about 60–70% of patients choose HD and 30–40% CAPD. In the UK as a whole, patient choice is often limited, with as many as 50% of dialysis patients on CAPD, and availability and uptake are variable throughout the country [Department of Health 1996a]. Some of this depends upon distance of residence from a renal unit [Dalziel and Garrett 1987; Boyle *et al* 1996], and this needs to be addressed by the establishment of additional units, usually of a satellite or low dependency type.

3.3 The pressure to accept more new patients with ESRF within an ever tightening fiscal environment leads to clinical compromise, including (for example) a reduction in duration of HD treatments, such as a change from thrice to twice weekly HD. A continuing decline in the number of hours of HD that European patients receive has been reported [Geerlings *et al* 1994], even when thrice weekly dialysis is employed. The dangers involved in this reduced quantity of dialysis became manifest in the United States in the 1980s, when concern over the mortality rate in dialysis patients resulted in the introduction of a framework of quality standards which are now monitored as part of the Medicare reimbursement system under the auspices of the Health Care Financing Administration [1990]. This led to an increasing awareness of the need to provide care within a framework of quality guidelines.

3.4 The provision of adequate choice and adequate quantities of dialysis has obvious cost implications which will need to be discussed with purchasers. Savings apparently achieved by what amounts to inadequate treatment may in the long run be more expensive, because of intercurrent illness and increased admission rates, which are in any case higher in patients with ESRF than in those with comparable chronic diseases [Thamer *et al* 1996].

■ ***The cheapest patient is usually a fit, well-treated patient, even if immediate costs may appear to be higher [Hornberger et al 1993b]***

Setting of minimum standards

3.5 We feel that guidelines couched in moderate language will be more helpful than rigid, prescriptive standards. In some areas, the concept of a minimum standard seems acceptable, as is the principle of recommending a higher target standard in some cases. These topics are discussed further in Appendix 4. No matter what the current recommendations may be, it is certain that standards will be refined and revised through the evolution of comparative audit. This standards initiative is thus linked to the work being done by the Registry Subcommittee of the Renal Association which has the remit to develop mechanisms for collecting and comparing patient data nationally. This process is already possible in transplantation since the UKTSSA possesses national data on transplant outcomes [United Kingdom Transplant Service Special Authority 1995b].

Context of the 1990 NHS reforms

3.6 The standards and subsequent audits set out in this document are consistent with the ethos of the NHS reforms set in train following the 1990 Act. However, quality of care cannot be guaranteed unless the purchasers agree to meet the necessary costs, which in most cases will be higher than those of less satisfactory care. As we emphasise again below, investment in better care will often lead to savings owing to reduction in complication rates and hospital admissions; this important aspect of care requires detailed study in many areas.

4 Specific practical aspects of comparative audit

Defining the population

4.1 As mentioned in paragraphs 1.6 and 1.7, standard setting and comparative audit will be meaningful only if they are carried out in a well defined population of patients. We lack internationally agreed definitions. In particular, *there is no standard definition of the point at which an end stage renal failure (ESRF) patient enters the renal replacement programme, particularly if he or she presents as a uraemic emergency* [Khan *et al* 1995; Bhandari and Turney 1996]. In addition, some studies are based on incidence and prevalence in a total population >0 years of age, others in adults only, variously defined as those over 15 or over 18 years of age.

Definitions of ESRF

4.2 ESRF may be defined in a number of ways, one of which is a creatinine clearance of <10 ml/min (ie 10% of normal function) or a sustained plasma creatinine concentration above 500 μmol/l. This low level of function is usually associated with uraemic symptoms and is an indication for starting dialysis, though the time chosen to start dialysis is also influenced by such factors as age, nutrition, comorbid conditions and cause of ESRF. Calculations of renal urea removal may help in deciding [Tattersall *et al* 1995]. Once a planned decision to start dialysis is made it is usually continued uninterrupted, and the date of initiation is therefore clear [Hakim and Lazarus 1995].

Late referral and emergency presentation

4.3 The situation is more complicated if the patient presents in advanced renal failure [Eadington 1996], and even worse if he or she presents as an emergency and requires resuscitation, investigation and rehabilitation before acceptance into a programme. We propose that, for patients who are initially treated as acute uraemic emergencies but are subsequently shown to have ESRF, the date of the first dialysis should be deemed to be the point of entry into the renal replacement programme, as it is for patients who enter the programme in a planned manner. This group of patients presenting as emergencies has been shown to have a poorer survival and greater morbidity [Ratcliffe *et al* 1984; Jungers *et al* 1993; Byrne *et al* 1994; Eadington 1996], some dying before 90 days of dialysis have been completed [Khan *et al* 1995]. This emphasises further the need to identify individuals in ESRF within the general population at an early stage (see Chapter 10 and Appendix 1).

4.4 Some patients undergo repeated admissions during the first few months of treatment, sometimes requiring short periods of dialysis, before becoming permanently dependent on outpatient dialysis. The start of uninterrupted dialysis should then count as the initiation date.

The '90 day rule'

4.5 In the United States it is unfortunate that patients are regarded, for reimbursement purposes, as being on the dialysis programme 90 days after being transferred to a free-standing renal unit or 90 days following the first dialysis. The

Medicare system starts complete reporting of patient data only at day 91, as does the US Renal Data System (USRDS) which includes hospitalisation rates and mortality (using this 90 day rule). We believe that it would be a wasted opportunity of audit if the UK dialysis programmes could not be compared directly with the US data. For this reason the standards outlined in this document for haemodialysis (HD) and CAPD suggest collection of data at 90 days as well as from the commencement of dialysis.

4.6 However, we emphasise the importance of medical care, dialysis needs and outcomes during the first 90 days, since it has been demonstrated [Khan *et al* 1995] that significant mortality and substantial morbidity, together with associated costs, occur during this period. The status for statistical purposes of those who die during the first 90 days after starting dialysis and who may have ESRF, but present as acute uraemic emergencies, remains unclear. In some cases the true nature of the disease may be revealed only at post-mortem examination. For the moment we recommend that their numbers be recorded.

Recommended standard

Analysis of data on ESRF treatment should be undertaken both from the point of initiation of uninterrupted dialysis and at the 90 day time point. (**B**)

4.7 This will render it possible to make a more accurate assessment of morbidity, outcome and hence costs in the first 90 days. In those presenting as acute uraemic emergencies, the cost implications are considerably higher than those of patients admitted electively to the ESRF programme and will need to be emphasised to purchasers [Campbell *et al* 1989; Jungers *et al* 1993; Khan *et al* 1995; Muirhead and Blyndal 1995].

How many patients can benefit from treatment for ESRF?

4.8 In the UK the annual incidence of new patients who can benefit from renal replacement therapy (RRT) is *at least* 80 per million population (pmp) [Feest *et al* 1990; McGeown 1990], but this figure is already exceeded in predominantly Caucasian populations in both Scotland and Wales, and a figure of 100 pmp may be more appropriate. In areas where there is a substantial population of certain ethnic minorities, and if patients aged over 80 are considered, the figure is much higher, since the incidence and prevalence of ESRF is 3–4 times higher in British populations of Afro-Caribbean and Asian origin [Roderick *et al* 1994, 1997; Department of Health 1996a; Raleigh 1997] and the incidence of renal failure rises steeply with age. *Age (even >80 years) is not of itself a contraindication to dialysis therapy*; the decision to offer therapy must be based on clinical considerations, particularly the general condition of the patient.

4.9 There is mounting evidence that the small number of renal treatment units in the United Kingdom leads to lower acceptance rates in part because the further the patient is from a renal unit the less likely he or she is to be accepted for ESRF treatment, especially in rural areas [Dalziel and Garrett 1987] and above all in the elderly [Boyle *et al* 1996].

Recommended standard

To achieve as a minimum an annual acceptance rate of new patients with renal failure of 80 pmp, *adjusted upwards as necessary for ethnic and age distribution of the population.* (**B**)

In smaller units year-on-year fluctuations may be greater in pmp terms than in larger units, and the means of several years will be the appropriate statistic.

Definitions of comorbidity and comorbidity scoring

4.10 The cost of treatment is heavily influenced by the fitness of patients on renal replacement therapy for all aspects of renal failure services, both dialysis and transplantation. Comparative audit and setting of standards must take account of factors other than those of the renal disease itself. Survival on RRT is strikingly influenced by age, diabetes mellitus, ischaemic heart disease, congestive heart failure and peripheral vascular disease [Keane and Collins 1994]. A system for measuring such comorbidity would be valuable, and a number of approaches have been proposed [Khan *et al* 1993; Keane and Collins 1994]; this is discussed further in Appendix 4. In a review of renal services in England [Department of Health 1996a] completed in 1994, age and diabetes mellitus were taken into account, after an extensive study of the database of the European Renal Association had identified a simple risk classification into three groups of patients:

Standard risk:	non-diabetics under 55
Medium risk:	non-diabetics 55–64; diabetics 15–54
High risk:	non-diabetics 65 and older; diabetics 55 and older; all HIV positive patients

The median survivals for each of these groups after the first year were 14.2, 7.4 and 3.5 years respectively. It must be emphasised that *the presence of comorbidity is not a contraindication to treatment.*

4.11 It should be possible to calculate for each patient a risk index incorporating these and other variables; future editions of this document will address this in more detail. In the meantime these recognised major risk factors should be recorded in audit data. (See Appendix 4 for further discussion of comorbidity.)

Supporting evidence

4.12 Setting standards for activities for which the evidence of benefit is equivocal remains contentious. We have reviewed several problem areas in some detail and concluded that the balance of evidence favours the need for the standard we propose. Our recommendations are preceded by an explanatory note. In these cases, as the evidence is not conclusive, interpretation must be circumspect.

Methodology

4.13 In some instances it is necessary to specify methods when setting standards or conducting comparative audit of process or outcome. An important example is urea kinetic modelling in dialysis, which is addressed in detail in Appendix 4 (A4.3). The problems of defining the start of regular dialysis, and the substantial early mortality ignored by the 90 day rule, have been discussed above.

Choice of therapy in ESRF

4.14 In making the appropriate choice of therapy, *patient preference must be considered after informed guidance on options*, taking into account medical and surgical contraindications. This policy almost certainly will increase further the already increasing demand for maintenance HD, particularly in-centre HD, which has obvious planning, staffing and cost implications. *However, equity of access is a fundamental principle of the NHS and can only be exercised if all modes of renal replacement therapy are readily available*. This need cannot be overemphasised, and the service will need to be structured to accommodate it. This has both short term and long term cost implications, since some treatments are more expensive than others.

Decision to withdraw or not to initiate dialysis

4.15 Debate continues as to whether these topics can be considered together or whether they present fundamentally different problems [Kjellstrand *et al* 1994; Moss 1994]. We have chosen to deal with them together since, at a practical level, the problems and processes of management they present are so similar.

Withholding dialysis

4.16 When a patient with ESRF has been referred for possible treatment, there may be circumstances in which the nephrologist will have reason to doubt whether it is best for the patient to begin or continue renal replacement therapy [Feest *et al* 1990; Hirsch *et al* 1994; Sessa 1995], often because of major comorbidity and lack of support. This problem is becoming particularly evident as a greater proportion of older patients, or patients with additional physical or mental problems, are taken on to treatment for ESRF. Patients may refuse or accept dialysis treatment without an adequate comprehension of what it will involve for them and their families. Sometimes dialysis will be initiated in the belief that the patient has a reversible acute renal condition, whereas irreversible renal failure will be present or appear [Bhandari and Turney 1996].

Deterioration in patients on dialysis

4.17 An even more difficult problem arises when a patient who is to begin with physically in relatively good health later suffers some disaster, for example a major stroke, which renders dialysis difficult and greatly lowers his or her quality of life. More often the problem is that a patient who is fit and competent allowing for age deteriorates gradually, both physically and mentally, until perhaps frank dementia becomes evident. Withdrawal from dialysis is now one of the major causes of death (20–25%) in dialysis programmes in the United States [Neu and Kjellstrand 1986; Port *et al* 1989; US Renal Data System 1995]. The USRDS US data [1995] show a withdrawal rate of 81.5/1,000 patient-years for white and 34.2/1,000 for black patients over the age of 65 years, almost half the total death rate; surprisingly, there was no difference between diabetic (64/1,000 patient-years) and non-diabetic (69/1,000 patient-years) patients. The main reasons given were failure to thrive or major additional problems.

4.18 This pattern is not apparent in all countries, however, even with a similar proportion of aged patients on ESRF treatment; see Catalano [1995] for review. Data are scanty for the United Kingdom; however, Catalano *et al* [1996] reported that withdrawal accounted for 17% of their dialysis deaths in Newcastle. A major problem lies in the reporting of 'cause of death'. If treatment has become ineffective, its withdrawal is a reasonable as well as humane act, and the cessation of treatment is not in itself the cause of death but rather a *mode* of death of which the *cause* is uraemia.

Thus there is a reasonable tendency to avoid the blunt statement that dialysis was withdrawn, and reported data are flawed and often not comparable either within or between countries, as is well known to be the case for statistics relating to suicides.

Principles of action

4.19 We do not believe it either possible or appropriate to lay down specific criteria for *not* dialysing patients. However, certain principles can be stated and a process recommended [Kjellstrand *et al* 1994; Mallick 1995].

- The purpose of beginning dialysis in patients with ESRF is to allow survival with a quality of life acceptable to the individual for a reasonable period; this has no agreed definition, but one can suggest 3 months as the minimum period. Dialysis is not intended primarily as a means of delaying proximate death.
- The interests of the patient are paramount.
- The decision not to institute or not to continue dialysis should not be influenced by the threat of litigation or availability of resources. We recognise that the issue of available resources and clinical priorities will be paramount during the next few years. We are committed to a constructive debate with purchasers on criteria for acceptance to dialysis.
- The opinions of relatives should be sought but should not be binding; it is best if they are approached initially by the patient in person, if this is possible.
- The physician must be satisfied that there are no reversible conditions present, eg extreme uraemia or depression, which might influence both patient and doctor to recommend not beginning or not continuing dialysis.
- When there is doubt the default option should be to offer a 'trial of dialysis'.

The decision whether or not to continue treatment is even more difficult, but the same principles of action apply. In this case the default option is to continue dialysis for a defined period and reassess the situation.

The process

4.20 Who should judge whether to withhold or withdraw dialysis, on what grounds, and how should the process be conducted?

- The consultant must solicit the views of the patient's family doctor, next of kin and other carers within the team. *It should be usual practice that the consultant discusses the patient's prospects with colleagues, senior nursing staff, social workers or counsellor before coming to a decision*. Often the patient's dilemma will be the subject of discussion at a unit clinical meeting or a case conference.
- The decision finally will be made by the consultant to whom the patient has been referred, who must assess the patient personally; *responsibility for the assessment must not be delegated*.
- The consultant will *inform the patient* of his/her options [Cohen *et al* 1993, 1995; Singer *et al* 1995] wherever this appears possible without causing undue distress. The most realistic and accurate description and prediction of the consequences of starting or not starting, or continuing or not continuing, dialysis should be given. If the recommendation is not to start dialysis, or to discontinue it, the

reasons must be given. The substance of this consultation must be recorded in the patient's notes.

- A major problem with patients who are dementing is that they have intermittent periods of lucidity and periods of incomprehension. How competent the patient may be to participate actively in the decision to withdraw dialysis can be difficult to judge. The consultant should be *guided by the advice of relatives but not bound by them*. As before, in situations of doubt, the default mode of behaviour should be to continue dialysis.
- *No patient should be abandoned* because dialysis is not to be initiated or not to continue. The decision to withhold or withdraw dialysis is a management decision which should be followed by a management plan that allows continued support in the best of circumstances *from the patient's point of view*, and finally death with dignity. This will often involve cooperation with palliative care teams or their equivalent.

Recommendation

The decision not to begin dialysis, or to discontinue it, ideally should be made jointly by the patient and the consultant nephrologist after consultation with relatives, the family practitioner and members of the renal unit multidisciplinary team. If the patient is unable to express a decision, the consultant should reach a decision guided by the principles outlined above. The decision and the reasons upon which it was reached must be recorded in the case notes. **(C)**

Items for audit

4.21 Items for audit should include the numbers of patients proposed for dialysis but not accepted for treatment each year, and the numbers of patients from whom dialysis treatment is withdrawn as a percentage of total deaths each year and as a death rate (pmp) of patients at risk.

5 Recommended standards for haemodialysis

Biomedical equipment

5.1 All haemodialysis (HD) equipment should comply with the relevant European safety standards. For HD machines the current standard is IEC 601-2-16 (1989) which is equivalent to BS 5724: Section 2.16 (1989).

Dialysers and disposable components

5.2 The current standards for dialysers and the extracorporeal circuit are ISO 8637 (1989) and ISO 8638 (1989); the equivalent British Standard is BS 7297: Parts 1 and 2 (1990). Where possible, disposables should be purchased from suppliers registered with the Department of Health Manufacturers Registration Scheme.

5.3 When selecting machines and dialysers, providers should use the manufacturer's specifications and the Department of Health evaluation reports to ensure that the performance of the equipment meets the requirements of the renal unit. Renal units should move towards the replacement of older machines with modern systems having facilities for producing bicarbonate based dialysate and for volumetric control of ultrafiltration (fluid removal during dialysis).

Reprocessing/ re-use

5.4 Although commercial dialysers are intended for use once, the reprocessing of dialysers for re-use in an individual has been incorporated into dialysis practice to differing extents in different countries for many years. It is not widespread in the UK, but the practice of re-using dialysers for an individual patient is growing. We accept that the repeated use of a dialyser in the same patient is an economic necessity when using expensive high flux membranes; already in 1993 in the United States, 88.5% of such dialysers were re-used. In addition, the financial pressures currently being experienced may encourage re-use even of standard membrane dialysers; in the United States in 1993, 68% of standard cellulosic membrane dialysers were re-used [US Renal Data System 1996]. We accept that there are strong environmental arguments for reprocessing disposable medical equipment.

5.5 However, it should be remembered that this behaviour must adhere to the Device Bulletin MDA-DB 9501 (obtainable from the Medical Devices Authority, Hannibal House, Elephant and Castle, London SE1 6TQ) which recommends that devices upon which the manufacturer has put the label 'for single use only', or equivalent, should be reprocessed only:

- If stringent requirements are met that the reprocessed item is safe and retains its integrity; all dialyser reprocessing (re-use) equipment should comply with the safety standard for electrical laboratory equipment BS EN 61010-1 (1993), and should be installed and used according to procedures that meet the Control of Substances Hazardous to Health (COSHH) regulations.

- If the unit can produce documentary in-house proof of validation studies demonstrating that the reprocessed item remains fit for its intended purpose, ie dialysis performance is not adversely affected.
- If there is a system of recording the reprocessing, for subsequent retrieval in the event of device failure and/or patient injury.

5.6 At the moment therefore we cannot recommend standards for reprocessing, but important items of information to be audited are:

- Quality of water used for reprocessing the blood compartment (which should be purer than for dialysis itself; see 5.14).
- Demonstration that the blood compartment has been washed free of the sterilising agent before re-use.
- Confirmation that the volume of the blood compartment has not been compromised, eg by fibrin clots.

In addition, the publication *Re-use of hemodialysers* (2nd edition) of the Association for the Advancement of Medical Instrumentation (AAMI) (3330 Washington Blvd, Suite 400, Arlington, VA 22201-4598, USA; fax: 00 1 703 275 0793) can be consulted.

Water for dialysis

Inorganic contaminants

5.7 Drinking water standards are not adequate for HD since the blood of patients is exposed to many thousands of litres of dialysis fluid annually, separated only by a thin membrane. In the USA a quality standard developed by the AAMI [1982] has been in place for over 10 years. Acceptable levels for impurities in treated water entering the dialysis unit are listed in Appendix 4 (A4.2), including trace metals such as aluminium which has been proven to carry special risks for dialysis patients. We recommend the adoption of this standard without modification.

- ***Recommendations on test schedules are included in Appendix 4.***

Microbiological contaminants

5.8 Bacterial contamination of dialysis fluid remains an important problem in routine HD and may be associated with pyrogenic reactions. While technical advances such as reverse osmosis (RO) have improved the situation, the increasing complexity of the fluid pathway in dialysis machines and the revival of bicarbonate buffer which favours the growth of bacteria have both exacerbated the problem [Ebben *et al* 1987]. Furthermore, new 'high flux' membranes with higher permeability than standard cellulosic membranes (eg Cuprophan^{TM}) and the use of water for reprocessing components of the extracorporeal circuit (re-use) demand more stringent attention to water quality.

5.9 Evidence from the USA suggests that pyrogenic reactions still occur, but it remains unclear whether the use of high flux dialysis or re-use are independent factors in their occurrence. The evidence suggests that intact bacteria and endotoxin (potent pyrogenic materials arising from the outer layers of bacterial cells) carry risks for patients no matter what membrane is used [Tokars *et al* 1994]. It is gener-

ally accepted that the ideal would be to use bacteria free, non-pyrogenic fluid for all dialysis procedures [Colton 1987].

5.10 In recent surveys non-compliance with the AAMI microbiological standards, which were set at 200 colony forming units (Cfu) per ml for water and 2,000 Cfu/ml for dialysis fluid, occurred in a significant number of samples from renal centres both in the USA and in Germany [Klein *et al* 1990; Bambauer *et al* 1994]. There was variable contamination in individual centres over time. To complicate the issue, standardisation of specialised culture techniques tends to be poor [Harding *et al* 1990].

5.11 Despite these difficulties, in the first edition [Renal Association 1995] of this standards document we accepted the AAMI standards for bacteria, and suggested that the AAMI standard for endotoxin in re-use water should also apply to dialysis fluid. Combined RO plus deionisation has been reported to give the best results for both endotoxin and bacterial counts [Laurence and Lapierre 1995].

5.12 Recently the AAMI standards have been criticised as being too lenient with regard to bacteria and it has been further suggested that the LAL assay used for detection of endotoxin (mainly lipopolysaccharide) is too insensitive to detect other low molecular weight cytokine-inducing pyrogens which are able to penetrate all dialysis membranes [Lonnemann *et al* 1996]. We are also aware that the European Pharmacopoeia (1992) recommends more stringent standards for microbial contamination (<100 Cfu/ml) and bacterial endotoxin (<0.25 Iu/ml) {Iu (international unit) ≈ Eu (endotoxin unit)}.

5.13 We suggest an increase in the stringency of the standards for dialysis fluid both with respect to microbial counts and for endotoxin. We await more scientific evidence on low molecular weight cytokine-inducing pyrogens before recommending more stringent LAL standards for endotoxin or recommending the change to a more sensitive methodology.

Recommendation

	Endotoxin (LAL)	Microbial count (TVC)	
Water for dialysis and dialysis fluid	<0.25 Eu/ml	<100 Cfu/ml	(**B**)

LAL = Limulus amoebocyte lysate test; TVC = total viable count of bacteria

■ ***Recommended methods and test schedules are discussed in Appendix 4.***

Water for dialyser reprocessing (re-use)

5.14 The quality of the water used should be high. We now recommend more stringent criteria for water used in rinsing the dialysis compartment.

Recommendation

	Endotoxin (LAL)	Microbial count (TVC)	
Water for dialyser reprocessing	<0.25 Eu/ml	<100 Cfu/ml	(**B**)

Biocompatibility issues

Bicarbonate dialysis fluid

5.15 One of the functions of the human kidney is to regenerate bicarbonate. HD replaces this function by including a supraphysiological concentration of base in the dialysis fluid. Bicarbonate, the natural body buffer, was the obvious choice as the base in the early days of the therapy. However, there were significant technical problems with its preparation and delivery. In the mid-1960s the introduction of acetate, which is metabolised to bicarbonate, solved many of these problems and provided the cornerstone for the worldwide expansion of dialysis.

5.16 The disadvantage of acetate became apparent a decade later when improvement in the efficiency of dialysis revealed the potential for overwhelming the capacity of some patients to metabolise acetate. Although no increment in patient survival has yet been demonstrated using bicarbonate rather than acetate, bicarbonate has been widely accepted as the buffer of choice; a number of studies over two decades [eg Graeffe *et al* 1978; Velez *et al* 1984; Hakim *et al* 1985], many involving short duration high flux dialysis, have shown less severe metabolic disturbance associated with the use of bicarbonate, leading to fewer intradialytic symptoms and thus to increased patient comfort during and after the HD session. It is not clear whether these data can be applied to conventional longer dialysis using cellulosic membranes. In this connection, however, we note the continuing trend towards short dialysis in Europe [Geerlings *et al* 1994]. In sum, although firm evidence is lacking and more data are needed, we feel that the shift to bicarbonate dialysis should continue. Bicarbonate is mandatory if there is evidence of liver disease or when dialysis is carried out in short, powerful sessions.

Recommendation

Renal units should move towards universal availability of bicarbonate and phasing out of acetate as the routine buffer base in haemodialysis fluid. (**B**)

Dialysis membranes

5.17 The use of synthetic membranes which can have more porous characteristics (high flux) than standard cellulosic membranes started in the mid-1980s with a view to increasing the depurative capacity of HD. Interest was heightened by the subsequent discovery that a number of these membranes (eg polysulphone, polyamide, polyacrylonitrile) had markedly less ability to activate complement and other cellular elements than standard cellulose. It was then postulated that this enhanced 'biocompatibility' might favourably influence the natural history of beta-2 microglobulin (β2M) associated amyloid bone disease which is now recognised as

an inevitable complication of standard dialysis using cellulosic membranes. This is a major problem, since clinical evidence of this condition typically appears after approximately 5 years of therapy, beyond which time there is an almost linear increase in the prevalence which reaches nearly 100% after 20 years of treatment [Floege and Ehlerding 1996].

5.18 There is evidence that long term treatment with synthetic high flux membranes may confer some beneficial effect on several, though not all, β2M amyloidosis associated symptoms [Van Ypersele de Strihou *et al* 1991], but the results of long term observations are awaited. Other reputed advantages include improved lipoprotein profile [Josephson *et al* 1992; Seres *et al* 1993] and improved systolic cardiac function [Churchill *et al* 1993], less severe intradialytic symptoms [Churchill *et al* 1993], less propensity to infections [Vanholder *et al* 1991; Hakim *et al* 1994a], and better nutritional indices [Parker *et al* 1996], but no improvement in survival on long term dialysis compared with cellulosic membranes has been reported in controlled studies, although some data suggest that an effect may be present [Hakim *et al* 1996].

5.19 On the other hand, these membranes involve considerably higher costs and they permit back-filtration with an increase in pyrogenic reactions (and thus require purer water). There is also a need for precise ultrafiltration control, which is far from universally available, and there are penalties from the loss of some solutes, such as amino acids, which it is desirable to retain. More data are required in this area.

Recommendation

Although the potential benefits of synthetic high flux membranes are recognised, we feel that it would be inappropriate to set a standard for membrane type at this stage. Equally, flexibility should be preserved and contracts that restrict patients to the use of cellulosic membranes for many years should be avoided. **(B)**

Clinical standards and targets

Adequacy of dialysis

5.20 Uncertainties about the reliability of dialysis, the response of the patient to the procedure and pathophysiological changes within the patient require that some objective measurements of the adequacy of dialysis delivery in achieving clinical goals be made regularly. *Monitoring the adequacy of dialysis treatment involves a global assessment*, which includes clinical assessment and objective measurement, including weight, blood pressure and laboratory investigations, together with some measure of the amount of solute cleared during the dialysis process. Adequacy must not be equated to quantity of dialysis alone.

Quantification of dialysis delivered

5.21 The molecular weights of the solvent and solutes to be cleared range over three orders of magnitude, from small (water, urea) to large (β2M), and clearance of the whole range of molecules by dialysis is important. However, for practical reasons most attention has been paid to small, easily measured solutes such as urea.

Clearance of low molecular weight solutes

5.22 Traditionally, pre-dialysis concentrations of urea and creatinine in the blood were used to measure the delivery of dialysis, with the implication that the lower the concentrations the better the dialysis. This approach has now been discredited, and

these measures can be misleading, particularly in the elderly and in poorly nourished patients. One large study [Lowrie and Lew 1990] demonstrated a *higher* mortality rate in patients with low pre-dialysis levels of these solutes. Over the past few years, ample evidence, some of it from controlled trials and prospective studies, has accumulated that good survival can be correlated with adequate removal of low molecular weight toxins for which urea is a surrogate — the more removed, in general, the better [Lowrie *et al* 1981; Hull and Parker 1990; Hornberger *et al* 1993a,b; Parker *et al* 1994]. These studies have not taken comorbidity into account, however, and it must never be forgotten that urea is only a non-toxic marker for other metabolites accumulated in uraemia.

5.23 Two methods of assessing the removal of urea are in current use (see Appendix 4 for details):

- The *urea reduction ratio* (URR) [Lowrie and Lew 1991] is the simplest. The percentage fall in blood urea effected by a dialysis session is measured, and this simple ratio has been shown to correlate with patient survival [Owen *et al* 1993].
- *Urea kinetic modelling* (UKM) is a more sophisticated method in that, in its full form, it takes account of the patient's own residual renal function, thus allowing more individualisation of the therapy. It takes account also of the re-equilibration of urea throughout the body after dialysis and urea generation between dialyses.

5.24 The *normalised 'cleared' volume, Kt/V*, during dialysis, derived by Gotch and Sargent [1985], has become a popular way of assessing quantity of dialysis; it relates the mass of urea cleared to the mass of urea present in the patient, where K is the total urea clearance rate, t is the number of minutes of dialysis and V is the urea distribution volume within the patient. When Kt/V is used to monitor and quantify dialysis, it is calculated like the URR from pre- and post-dialysis concentrations, and it is not necessary to know K or V.

5.25 However, there is no internationally agreed best method for measuring Kt/V in everyday clinical practice, and more than six methods are commonly in use in renal units throughout the UK at the moment. This is important, since different formulae applied to the same data give different Kt/V; see Appendix 4 and Movilli [1996] for review. There are also major inherent inaccuracies in the measurement of Kt/V whatever methodology is used to calculate it, and the recommendations below must be viewed in the light of these problems, which are discussed in greater detail in Appendix 4. *Thus it is important that the method used to calculate Kt/V should be recorded when comparing, presenting or submitting data.*

5.26 Despite these problems, we recognise the necessity to replace traditional methods with these approaches, and also recognise the progress made by the Health Care Financing Administration which has developed criteria that dialysis facilities must meet to qualify for Medicare funding. Our recommendations parallel the evolution of standards in the USA [eg Renal Physicians' Association 1993; Gagle 1995].

5.27 Finally, although historical comparative information is flawed, with no controlled and case-matched data, world experience and attitudes to dialysis adequacy are based on the belief that three sessions of HD per week is the minimum necessary to maintain health, save in exceptional circumstances. In addition, thrice weekly dialysis leads to fewer post-dialysis symptoms, and results in better plasma biochemistry and blood pressure readings than twice weekly dialysis.

Recommended MINIMUM standard

Every patient for thrice weekly haemodialysis should show:

EITHER Stable URR >65%

OR Stable *Kt/V* >1.2 (dialysis and residual renal function)

The method used to calculate *Kt/V* must be noted alongside any data. **(B)**

If a patient is found to be receiving less than the target amount of dialysis, steps should be taken to increase this by increasing the duration of dialysis (the most effective), or increasing dialyser surface area, or increasing blood flow and/or dialysate rate.

■ ***Methodologies are outlined in Appendix 4 along with discussion of the shortcomings and errors inherent in each approach.***

5.28 It should be noted that these recommendations are *individual targets which each patient should reach or exceed*; the *mean Kt/V* for a renal unit's patients in aggregate will of course be higher than 1.2 — perhaps 1.35–1.45. Whether particular subsets of patients should have a higher target *Kt/V* will emerge as data accumulate.

5.29 It is not clear yet at what point further increase in *Kt/V* fails to lead to an increase in survival or well-being; probably this lies around a *Kt/V* of 1.5–1.7 [Charra *et al* 1992; Hornberger *et al* 1993a,b]. Cost-benefit analysis shows that an increase in *Kt/V* from 0.7 up to 1.5 not only produces a steady improvement in quality adjusted survival but also a fall in lifetime treatment costs, mainly because of decreased hospitalisation [Hornberger *et al* 1993b]. Prospective but uncontrolled studies [Parker *et al* 1994; Yang *et al* 1996] demonstrated a fall in mortality following an increase in delivered *Kt/V*.

Twice or thrice weekly HD?

5.30 The mean number of dialysis sessions carried out per patient per week is 2.90 in the USA and 2.88 in Europe. Virtually all understanding of dialysis adequacy stems from research or observation in patients dialysed thrice weekly; no adequate data comparing twice weekly with thrice weekly dialysis exist. We take the view that, while twice weekly dialysis may be necessary in some geographically remote areas, it should not be generally recommended except when there is good preservation of residual renal function, such as in the first year or so after starting dialysis early to avoid morbidity (see Chapter 9). The minimum standards for twice weekly dialysis are therefore theoretical, and not based on published data. *A stable URR >80% or a stable Kt/V >1.80 is theoretically necessary* [Gotch 1990]. These are difficult to achieve in many patients, and some residual renal function will usually be necessary to allow an adequate weekly *Kt/V*.

Recommendation

We recommend the adoption of thrice weekly dialysis sessions as a minimum in the majority of patients. If twice weekly sessions are imposed by geographical constraints, careful monitoring of the patients' nutritional status and dialysis adequacy must be undertaken. Where geographical constraints do not apply, the presence of significant residual renal function (glomerular filtration rate 5–10 ml/min) must be demonstrated in each patient. Slippage from thrice to twice weekly sessions to accommodate more patients in congested facilities is to be deplored. (**C**)

Clearance of high molecular weight solutes

5.31 A significant theoretical limitation in the URR and *Kt/V* concepts is that high molecular weight solutes are not considered. By implication, β2M is a uraemic toxin as it is recognised as the building block of dialysis related amyloidosis. It accumulates to high levels in dialysis patients and cannot be removed by standard dialysis membranes. Given the evidence, it seems logical to consider the removal of both high and low molecular weight solutes in the planning of dialysis. This is another factor contributing to the increased interest in high flux dialysis. However, even if high flux dialysis is used, special considerations are required to ensure efficient removal of high molecular weight solute such as β2M. Significant amounts can only be removed if filtration is combined with the diffusive process on which traditional HD is based. The combined process, known as haemodiafiltration, has gained recognition as a legitimate alternative therapy; indeed the major manufacturers of dialysis equipment are producing new machines specifically for this purpose, but it carries the penalty of very high cost.

While acknowledging this trend, we feel that it is too early to take a position on haemodiafiltration and its potential benefits. The advent of such therapies makes adherence to the strict water quality standards outlined above all the more necessary.

Correction of anaemia

5.32 As part of improved care of dialysis patients, the anaemia of chronic renal failure should be corrected, first by optimising dialysis and nutrition, but frequently the administration of recombinant human erythropoietin (EPO) will be needed. EPO should not be used, however, as reinforcement for inadequate dialysis [Ifudu *et al* 1996]. Although no relationship has been shown with survival, the haemoglobin concentration has a major impact on the quality of life, exercise capacity and sexual function in controlled trials [Eschbach 1989; Canadian Erythropoietin Study Group 1990]; anaemia has been shown to influence survival from cardiac causes [Harnett *et al* 1995]. Moreover, repeated blood transfusions cannot maintain haemoglobin at a constant level, may jeopardise future successful transplantation by sensitising the patient, and carry a risk of transmitting viral infections and causing iron overload. There is evidence also that immune responses are improved in dialysis patients treated with EPO [Birmingham *et al* 1996].

5.33 The use of EPO, however, carries with it major financial implications which will need discussion with purchasers. Guidelines for its use have been published previously by us, and further guidance documents are awaited from European (Biomed)

and American (National Kidney Foundation DOQI) bodies. Thus we make no detailed suggestions for the use of EPO or iron for the present.

Recommendation

A target haemoglobin concentration of not less than 10 g/dl (haematocrit >30%) should be achieved in the great majority (>85%) of patients after 3 months on HD. Transfusions should be avoided wherever possible in patients likely to be transplanted, to avoid sensitisation. (**A**)

■ ***Recommendations on how individual units should gauge their success or otherwise in achieving this target are given in the list of items for audit in Appendix 3.***

Correction of acidosis

5.34 The degree of pre-dialysis acidosis can reflect dialysis adequacy. In a retrospective uncontrolled study of patients dialysing thrice weekly, pre-dialysis bicarbonate concentrations below 17.5 mmol/l were associated with poor survival [Lowrie and Lew 1990]. Inadequate dialysis dose, twice weekly dialysis and the use of acetate in relatively short dialysis sessions can compromise bicarbonate delivery. Conversely, better correction of plasma bicarbonate is associated in the long term with decreased protein catabolism [Papadyannakis *et al* 1985] and slower progression of hyperparathyroidism [Lefebvre *et al* 1989], though the role of acidosis in renal bone disease remains controversial [Bushinski 1995].

Recommendation

A target pre-dialysis serum bicarbonate within the normal range quoted by the local pathology laboratory should be the aim in all patients after 3 months on HD. (**B**)

Nutritional status

5.35 Although a low serum albumin is only a surrogate index of nutrition, it is statistically a powerful predictor of mortality in dialysis patients [Lowrie and Lew 1991; Owen *et al* 1993; Bergström 1995]. While other comorbid conditions (eg infection) may affect serum albumin concentrations, and a direct causal relationship between *Kt/V* and serum albumin has not yet been proven, it is likely that a high prevalence of hypoalbuminaemia in a dialysis programme is most likely to reflect systematic underdialysis. It is recognised that hypoalbuminaemia in patients starting on regular dialysis can reflect severe malnutrition which has been present for a long period. This takes a considerable time to reverse, even with good quality HD and nutrition, which may need to include nutritional supplements and intradialytic parenteral nutrition for a period of time. These extra expenses will need to be incorporated into contracts [Kopple *et al* 1995a], and malnutrition at entry to dialysis avoided by good follow-up and early entry to dialysis wherever possible (see Chapter 9). Although no cost-benefit analyses have been done, it is possible that these expenses could be recouped owing to decreased morbidity and admission rates following start of dialysis.

Recommendation

Dietary intake of protein should be assessed regularly by a dietitian, and an intake of at least 1.0 g/kg ideal bodyweight for height/24 h achieved, with an energy intake of at least 35 kcal/kg ideal bodyweight for height/24 h. (**B**)

A target serum albumin within the normal range quoted by the local pathology laboratory in all patients should be the target after 6 months on regular HD. It is recognised that patients with intercurrent illness and some vegetarians may fall short of this, but the incidence of complications is itself an index of malnutrition. (**B**)

Since the figure for concentration of serum albumin varies considerably with the method used, this should be stated and local normal ranges established [Blagg et al 1993; Joseph et al 1996].

Blood pressure

5.36 Hypertension is common in chronic renal failure and in end stage renal failure patients. Left ventricular hypertrophy is common and is an independent predictor of cardiac death in dialysis patients [Silberberg *et al* 1989]. Hypertension is more common with short intensive dialysis than with longer slower dialysis [Charra *et al* 1992], so the control of hypertension by pharmacological means is of increasing importance.

5.37 The literature gives conflicting views on the importance of hypertension as a predictor of death in dialysis patients, a very low blood pressure being (as in the general population) a predictor of increased mortality. However, a growing body of evidence [Foley *et al* 1996] suggests that careful control is advisable, and indeed that a relatively low target blood pressure is desirable; see Ritz [1993] for review. However, it is recognised that the pre-dialysis blood pressure is often recorded at a time of maximal anxiety and fluid loading for the patient. This demands a relatively broad target.

Recommended standard

Target pre-dialysis blood pressures should be:

Age <60 — BP <140/90 mmHg (Korotkoff V if auscultation is used)

Age >60 — BP <160/90 mmHg (Korotkoff V if auscultation is used) (**B**)

For more accurate assessment of blood pressure status, ambulatory blood pressure monitoring is desirable.

Biochemical profiles

5.38 Electrolyte homoeostasis in dialysis patients is to some extent under the control of dialysis staff and is a marker for the quality of care given. It may also reflect the compliance of the patient with respect to diet and medications. In addition a high phosphate concentration drives hyperparathyroidism (see 5.39). Control of plasma phosphate concentration depends not only upon diet but on the selective use of phosphate-binding agents.

Recommended standard

The following are target ranges for pre-dialysis biochemical variables:

Potassium	3.5–6.5 mmol/l*
Phosphate	1.2–1.7 mmol/l
Calcium	total calcium within the normal range quoted by the local pathology laboratory, corrected for serum albumin concentration, or normal ionised calcium where available **(B)**

** It should be noted that in subjects on dialysis approximately 50% of potassium is dialysed, but the other 50% is excreted via the gut. A number of medicines, including angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory agents and beta-blockers, interfere with this secretion and cause hyperkalaemia even with an adequate restriction of oral potassium.*

Hyperparathyroidism

5.39 There is controversy as to what level of parathormone (PTH) in the blood should be maintained, and there are also methodological differences; today only an intact hormone assay is acceptable. Some maintain that the immunoreactive PTH (iPTH) should be kept within normal limits [Coburn 1993; Hutchison *et al* 1993; Connella *et al* 1996] but the general view is that this may lead to a proportion of patients developing adynamic bone. Whilst the clinical consequences of adynamic bone are not yet clear, the risks of hyperparathyroidism are well documented. For the moment we suggest that a somewhat less rigorous standard should be set which, as data accumulate, may need alteration.

Recommendation

iPTH (intact hormone assay) should be maintained at between 2 and 3 times the local normal range (130–210 pg/ml). **(B)**

Infection of patients and staff

5.40 The prevention of transmissible infections to patients and staff is dealt with in Chapter 11.

Counselling and social support

5.41 This chapter has identified a number of aspects important for the physical welfare of patients on dialysis. Equally important are the psychological and social welfare of the individual stricken with renal failure. Whilst it is not possible to set standards in this area, and staffing lies outside the purpose of this document, all renal units should have programmes for the education, counselling and social support of renal patients, particularly those in renal failure.

Vascular access for HD

5.42 Access to the blood stream for HD [Fan and Schwab 1992; Koo and Burnapp 1996], which has been referred to as the Achilles heel of dialysis [Kjellstrand 1995], is the major factor in the success or failure of the technique [Feldman *et al* 1996]. In the United States in 1991, 21% of all hospital admissions of HD patients resulted from problems related to access. Today fistulas may take the form of a subcutaneous arteriovenous fistula (Brescia-Cimino) either at the wrist in the anatomical snuff-box or at the elbow, grafts in the arm using synthetic materials such as PTFE, or

indwelling central venous catheters, usually placed in the subclavian vein under sterile conditions.

Provision of access

5.43 The quality of the vessels used is crucial to success; to this end the cephalic veins should be avoided for routine venepuncture in all patients likely to require long term access, and blood drawn elsewhere. Above all, the cephalic veins should not be used for intravenous infusions. Catheters should not be inserted into the subclavian veins, the jugular vein being used instead, because of the risk of subsequent stenosis in the subclavian leading to obstruction and venous hypertension during dialysis. Patients who have, nevertheless, had subclavian catheters in the past should have venograms; Doppler ultrasonography of this area is not adequate.

Many problems remain unsolved [Feldman *et al* 1996], which render the recommendation of standards in this area impossible until further data are obtained.

5.44 *Choice of initial procedure* is controversial. Whilst in the United States two-thirds to three-quarters of initial fistulas use synthetic materials [Himmelfarb and Saad 1997], in the United Kingdom it is usual to employ the patient's arteries or veins for the primary procedure, with over 90% success rate in many units [Koo and Burnapp 1996]. The wrist of the non-dominant limb is preferred unless the cephalic vein is poor, or the artery damaged or absent; if unsuccessful, the dominant limb may be used. The brachial vessels may be tried next, with or without a basilic vein transposition. Finally, PTFE may be employed in arm or leg if all else fails. Which patients would be better off having a PTFE graft as an initial procedure, and how they can be identified, remains unclear, although age, diabetes and female gender appear to be risk factors for early failure of autologous arteriovenous fistulas.

5.45 *Timing of access placement* is important; ideally this should be ready by the time the patient needs dialysis, which means that 4–12 weeks will be needed depending upon the technique used and the success of the initial attempt. In patients who present late or as uraemic emergencies, dialysis access will usually be by central catheter, and again the jugular is preferable to the subclavian because of the risk of subclavian vein stenosis.

5.46 *The surgeon* who performs the operation is a major variable in determining the primary success of arteriovenous fistulas [Prischl *et al* 1995].

Preservation of access

5.47 *The pathogenesis of access thrombosis* is becoming clear. Thrombosis of fistulas or A-V grafts appears to follow from turbulence, usually at the venous end of the fistula. This in turn leads to platelet deposition and activation, with release of platelet derived mitogenic factors. These lead to myointimal proliferation and stenosis, and finally complete occlusion with thrombosis occurs [Himmelfarb and Saad 1997]. How fistulas at risk for thrombosis should be identified by *monitoring* is not established [Besarab and Samarapungam 1997]; pressures, flows and recirculation can be measured directly, flow and turbulence visualised through colour Doppler techniques, or angiography performed. Which technique(s) are best has not been established.

5.48 *Antiplatelet agents or anticoagulants*. Whether these are effective in reducing thrombosis rates in PTFE grafts has been studied in controlled trials. Sreedhara *et al* [1994] demonstrated a reduction in both, using dipyridamole alone, whereas aspirin alone or together with dipyridamole *increased* complication rates. Thus the use of dipyridamole can be recommended in PTFE grafts until further controlled trial data accumulate, and aspirin should be avoided.

5.49 *Early or prophylactic treatment of stenosis*. If stenosis is identified, it is not clear whether angioplasty or refashioning, before thrombosis takes place, is preferable to waiting for those that will thrombose to do so [Besarab and Samarapungam 1997]. The role of stenting is still under evaluation. In the early diagnosis of stenosis, Doppler angiography is a valuable tool.

5.50 *Which treatment of thrombosis* to use is not clear: thrombolysis and/or surgical removal are available, alone or in combination. No controlled trial comparing these procedures has been performed.

Audit of access

5.51 No standards can be set at the moment for dialysis access, which is influenced by the case-mix of patients (eg proportion of diabetics and elderly patients with vasculopathy), but we suggest some items for audit in Appendix 3 (A3.1).

Outcome of patients on HD

5.52 We take the view that rather than examining survival in relation to treatment, or intention to treat, it is better to consider patients' survival as individuals no matter what treatments they may have received since entering end stage renal failure. Survival is of course strongly influenced by comorbidity [Khan *et al* 1996] and age [Valderrábano *et al* 1995], but complete data sets for the United Kingdom allowing for age and for comorbidity do not yet exist. In the meantime, data for treatment related and overall survivals for patients aged 18–55 years without systemic disease are given at the end of Appendix 3 (A3.8).

Recommendation

Survival data should be audited in individual units and synthesised by the UK Renal Registry. In the interim, the outcome results for UK patients in the ERA Registry should be used for setting standards and comparative audit.

Items for audit

5.53 A list of general items for audit in haemodialysis is included in Appendix 3.

6 Recommended standards for peritoneal dialysis

Introduction

6.1 A unit offering peritoneal dialysis (PD) should provide not only continuous ambulatory peritoneal dialysis (CAPD) but also automated peritoneal dialysis (APD), which includes continuous cycling peritoneal dialysis (CCPD), intermittent peritoneal dialysis (IPD) and nightly intermittent peritoneal dialysis (NIPD). It should have access to adequate back-up haemodialysis (HD) facilities and renal transplantation.

6.2 The unit should be aware of the limitations of CAPD and related techniques. In particular, in patients with large muscle mass and no or little residual function it may provide inadequate dialysis however the treatment regime is adjusted. It is, in contrast, particularly suitable for smaller patients taken on early with considerable residual renal function. We regard use of CAPD and related techniques in patients fundamentally unsuited to them for fiscal or organisational reasons as inappropriate and to be deprecated.

Biomedical equipment

6.3 All electromechanical equipment used to undertake PD should comply with national and international standards for electromechanical safety (IEC 601 Part 1). For PD equipment, the specific European standard is EN 50072 which incorporates the British Standard (BS 5724: Section 2.29 1992; equivalent to HD BS 5724: Section 2.16 1989). Such equipment should be purchased from manufacturers registered with the Department of Health Manufacturers Registration Scheme (IRC 9001).

Solutions for PD

6.4 Fluids for PD need to satisfy current European quality standards enshrined in the European Good Manufacturing Practice. The manufacturing facilities should also meet European standards (ISO 9001, ISO 9002, EN 46001, EN 46002). Product registration files must be registered with, and approved for clinical use by, the UK Department of Health Standards Body.

6.5 In selected patients, specialised solutions such as amino acid containing solutions or glucose polymers are preferable to standard solutions [Hutchison and Gokal 1992]. Other solutions with variations in the concentration of calcium, magnesium, osmotic agents and buffers also will be needed. Such solutions are likely to be more expensive, so their selective use should be reflected in negotiations with purchasers.

CAPD systems

6.6 Disconnect, 'flush before fill' systems are superior to earlier systems. In controlled trials their use results in a significantly lower incidence of peritonitis and a better quality of life [Maiorca *et al* 1983; Churchill *et al* 1989]. Such systems should be standard for all patients, unless they are incapable of managing this slightly more difficult technique. Extra costs should be partly offset by lower morbidity, hospital admission and peritoneal failure rates, as suggested by the study of Harris *et al* [1996].

Recommended standard

The use of disconnect systems should be standard unless contraindicated. **(A)**

Automated peritoneal dialysis

6.7 The use of cycling machines at home may be necessary for clinical reasons, for example, high transporter status of the peritoneum (10–15% of the dialysis population), those with impaired filtration, or for psychosocial reasons; these three groups together form 20–25% of the total CAPD population. Therefore APD should be available for selected patients. Monitoring of the dose of dialysis delivered is especially important in APD (see below and Appendix 4). Automated systems are more expensive than standard disconnect manual systems; their extra costs will need to be reflected in contracts negotiated with purchasers, but it should be noted that usually APD will be cheaper for these patients than the alternative, ie transfer to in-centre HD.

Recommendation

Automated peritoneal dialysis should be available as clinically indicated and not constrained by financial considerations. **(C)**

Clinical standards

6.8 The standards listed for patients on HD that apply equally to PD include:

- Correction of anaemia (see 5.32)
- Control of blood pressure (see 5.36)
- Prevention of transmissible infections to patients and staff (see Chapter 11)

Nutritional status

6.9 Protein malnutrition with low serum albumin is a powerful predictor of mortality in dialysis patients using CAPD as well as HD [Lowrie and Lew 1990; Owen *et al* 1993]. Additional losses not faced by HD patients are present: amino acids to the equivalent of 0.2 g/kg/24 h are lost in the dialysate together with 0.12 g protein/kg/24 h.

6.10 Although it is likely that a high prevalence of hypoalbuminaemia reflects underdialysis, a direct causal relationship between *Kt/V* (see 5.24 for definition) and serum albumin has not been proven. There is no one parameter that ideally measures nutritional status in a simple non-invasive manner, but skinfold thickness and mid-arm circumference, used alone or as part of a composite nutritional index, have been shown to be reasonable indicators in CAPD patients [Harty *et al* 1994].

6.11 Malnutrition can be recognised by a reduced serum albumin,* actual body weight <90% of ideal body weight for height, and estimated protein intake <0.8 g/kg ideal body weight for height/24 h [Kopple *et al* 1995b]. Every effort to promote nutrition by enteral or, if necessary, by parenteral routes is strongly recommended in such patients. Vegetarians in particular may show serum albumin concentrations lower than the recommended concentration.

* Since the concentration of serum albumin varies substantially with the method employed, the technique of measurement should be recorded in audit data [Blagg *et al* 1993; Joseph *et al* 1996].

Recommendation

A protein intake greater than 1.2 g/kg ideal body weight for height/24 h together with an oral calorie intake, including glucose absorption from the dialysate, of >35 kcal/kg ideal body weight for height/24 h should be attained by all patients. (**B**)

The serum albumin of at least 70% of patients should be within the local normal range (see Appendix 4 for expression of continuous variables). (**B**)

Biochemical profiles

6.12 Electrolyte homoeostasis in dialysis patients is to some extent under the control of dialysis staff and is an indicator of the quality of care given; however, dietary indiscretions and non-compliance also undoubtedly influence it. The ideal target concentration of calcium has not been established firmly. Since it is desirable to avoid the use of aluminium containing phosphate-binding agents, low calcium dialysate is becoming more popular.

Recommended standard

Potassium	3.5–5.5 mmol/l*
Phosphate	1.1–1.6 mmol/l
Calcium	within normal limits for local laboratory, corrected for serum albumin concentration, or normal ionised calcium where available (**B**)

** It should be noted that in subjects on dialysis approximately 50% of potassium is dialysed, but the other 50% is excreted via the gut. A number of medicines, including angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory agents and beta-blockers, interfere with this secretion and cause hyperkalaemia even with an adequate restriction of oral potassium.*

Hyperparathyroidism

6.13 Currently the estimation of immunoreactive parathormone (iPTH) by an intact hormone assay is the best non-invasive method for assessing parathyroid activity and renal bone disease. Values in excess of three times the upper limit of the normal range (10–70 pg/ml, ie >210 pg/ml) (1.1–7.4, ie >22 ng/ml) usually indicate parathyroid overactivity, whilst values of <50 pg/ml (5.3 ng/ml) suggest the presence of adynamic bone. The latter finding is commoner in CAPD patients than in those receiving HD [Sherrard *et al* 1993], but it is symptomless and its long term natural history is unknown; however, it is associated clinically with metastatic calcification, and biochemically with a relative inability to dispose of a calcium load [Kurz 1994].

6.14 As in patients receiving HD, there is controversy about how strictly the serum parathormone concentration should be controlled [Coburn 1993; Hutchison *et al* 1993], in view of the potential dangers of adynamic bone; the current consensus is that 'mild activity' is desirable.

Recommendation

iPTH (intact hormone assay) should be maintained at between 2 and 3 times the upper limit of the local normal range (130–210 pg/ml). (**B**)

■ ***Regular audit of these parameters will eventually permit calculation of the minimum desirable standard.***

Acidosis and alkalosis

6.15 Correction of acidosis is readily achieved in CAPD by the use of higher lactate or bicarbonate based PD fluids and of oral calcium carbonate as phosphate binder. A mild alkalosis may be seen in patients using low calcium dialysis fluid, the use of which avoids the need for aluminium containing phosphate-binding agents.

Recommended standard

The serum bicarbonate level should not fall below the local normal range, or rise more than 3 mmol/l above it. (**B**)

Peritoneal equilibration tests

6.16 A peritoneal equilibration test (PET) [Twardowski *et al* 1987] assesses the peritoneal membrane transporter status. It may be helpful in prescribing the appropriate PD regimen but is of limited value in prescribing the dose, and it takes 4–6 weeks after starting dialysis to stabilise [Rocco *et al* 1995]. Its main utility is in assessing peritoneal membrane function, in particular loss of ultrafiltration [Korbet and Roxby 1994].

Recommended standard

PET tests should be performed after 4–8 weeks on dialysis, when clinically indicated, eg when biochemical indices raise suspicion of changes in peritoneal transport characteristics, and annually as a routine. (**B**)

Adequacy of CAPD

6.17 We believe that the concept of adequacy is very important. It has been shown in prospective studies to be a predictor of outcome in new patients starting CAPD [Churchill *et al* 1996] and in patients already on CAPD treatment [Maiorca *et al* 1995; Ronco 1997]. As with patients on HD, adequacy is a *global concept*, involving various levels of measurement, which include clinical assessment of well-being and physical measurements, measures of small molecule solute clearance and fluid removal, and the impact of the treatment on the patient's life. It is important that clinical aspects be taken into consideration in arriving at targets of small molecule solute clearance, which in general are the basis for measuring dialysis dose.

Prescribing CAPD

6.18 Prescribing of dialysis dose and measuring of adequacy of dialysis are best done during the initiation phase immediately after starting CAPD, and in a subsequent phase when the dose is assessed and monitored. Since the PET test takes 4–6 weeks to stabilise (see above), values obtained earlier than this may not be representative of membrane transport characteristics. Hence the initial CAPD regimen should be prescribed assuming normal transport characteristics and in the light of measured residual renal function and maximally tolerated peritoneal dwell volume.

6.19 After 4–6 weeks a PET test should be done to assess peritoneal transport characteristics. Patients with high transport characteristics (who form a higher propor-

tion of patients in the UK than in studies from the United States) may not be suitable for standard CAPD exchanges, and will often require short-dwell APD. Those with low transporter status may be unsuitable for PD altogether, unless they have good residual function (see below). Subsequently the dialysis dose can be monitored on an annual basis or as indicated clinically.

Quantity of dialysis delivered

6.20 There is even less consensus than for HD about both the best methods to measure the dose of PD [Keshaviah 1994] and the link between dialysis dose and outcome [Blake *et al* 1991; Harty *et al* 1993; Churchill *et al* 1996]. In general, non-prospective data show that less may be worse, but as yet no data show that increasing small molecule solute clearance in PD patients beyond the standard four exchanges of 2 litres improves survival [Gokal and Harty 1996].

6.21 As for HD, the most favoured methods to assess dialysis dose in CAPD at the moment use small molecule solute clearances as a surrogate for the as yet unknown toxic metabolites accumulating in uraemia; *this may be even more inappropriate for CAPD than for HD because of the greater clearance for larger solutes that CAPD provides.*

Kt/V (urea) and weekly creatinine clearance

6.22 Nevertheless, the *weekly Kt/V for urea* (see 5.24 for definition of *Kt/V*) and the *weekly creatinine clearance* are both frequently used at the moment. Each is the sum of the clearance achieved by the dialysis and that due to the residual renal function. It should be noted that the expression of creatinine clearance (C_{cr}) in litres/week conceals just how marginal the achieved clearances are: 60 l/week represents less than 5.9 ml/min of creatinine clearance, 70 l/week <6.9 ml/min, and 80 l/week <7.9 ml/min. Furthermore, even on CAPD the glomerular filtration rate (GFR) falls from a mean of 4 ml/min at the start of dialysis to about 1–1.5 ml/min by 2 years [Churchill *et al* 1996], even though this rate of decline is much slower on CAPD than on HD [Lysaght *et al* 1991]. No data are yet available for decline in residual function on APD. *Thus, to achieve the same total small molecule solute clearance, the dialysis clearance will need to be increased, especially in those on dialysis for longer than 2 years or already anuric*. Also, the two measurements of small molecule solute clearance differ in their susceptibility to manipulation; in practice, creatinine clearance is much more difficult to increase than *Kt/V* for urea.

6.23 A weekly *Kt/V* <1.65 was reported to be associated with poor outcome [Blake 1993; Genestier *et al* 1995], and a weekly Kt/V >1.9 (dialysis + residual renal function) or total weekly creatinine clearance of >60 l/week/1.73 m^2 of body surface area has been advocated for standard CAPD [Churchill *et al* 1996], even higher clearances being suggested in recent publications [Blake *et al* 1996; Burkart *et al* 1996; Oreopoulos 1996]. Churchill *et al* [1996] reported a steady decrease in survival with lower initial creatinine clearances (including residual renal function), from 100 l/week (9.9 ml/min) to 30 l/week, but no clearances subsequent to those measured at the beginning of dialysis were reported in these patients.

6.24 It must be emphasised also that all these studies were based largely on theoretical predictions, even though these have been validated to some extent against actual experience [Vonesh *et al* 1996], and that there is no final proof that achieving these targets will result in improved outcome [Gokal and Harty 1996]. In the

CANUSA (Canada and US collaboration) study [Churchill *et al* 1996] three-quarters of the deaths during treatment within 2 years of starting CAPD were from cardiovascular causes, some in well dialysed patients.

Other modes of peritoneal dialysis

6.25 As mentioned in the introduction to this chapter (6.1), APD comprises a number of regimes involving varying amounts of fluid and dwell times (CCPD, NIPD, NIPD with 'wet' days, and tidal PD). There are few data on either solute clearances or impact on outcome of such regimes. If the hypothesis that peak concentrations of solutes are the most important proves to be correct, intermittent therapies will need higher targets for solute clearance [Keshaviah 1994].

6.26 Thus the recommendations given immediately below can be regarded merely as approximate targets for which to aim, which can be refined in the light of more data. *Again we emphasise that the general state of the patient must be taken into account when prescribing quantity of CAPD; a well nourished patient with good biochemistry and haemoglobin but apparently unsatisfactory clearance is more reassuring than an ill patient with poor metabolic control but apparently good clearance*. Finally, even though *V* is a function of body size, weekly *Kt/V* or total creatinine clearance needs to be prescribed on an individual basis [Hull 1996], especially with regard to the maximally tolerated volume of dialysate.

Recommendation

A total weekly creatinine clearance (dialysis + residual renal function) of 50 l/week/1.73 m^2 and/or a weekly dialysis *Kt/V* urea of greater than 1.7, checked 6–8 weeks after beginning dialysis, should be regarded as minima; *the MEAN Kt/V or clearance of a group of patients needed to achieve these minimum figures will be higher, eg Kt/V 1.9–2.0, creatinine clearance 60–65 ml/min*. These studies should be repeated at least annually, or if suspicion arises that residual function has declined more rapidly than usual. (**B**)

Values achieved using APD regimens are even less well defined, but almost certainly need to be higher than for CAPD: *minima* of *Kt/V* >2.0 and weekly creatinine clearance >60 litres should be aimed for. (**C**)

If an inadequate *Kt/V* or C_{cr} is identified, it is important to identify the cause(s) (poor compliance, hypercatabolism and malnutrition, decreased peritoneal clearance or falling residual function) so that appropriate action can be taken. This action may include:

- an increase in the volume of exchanges, eg from 2.0 to 2.5 or even 3.0 litres;
- an extra daily exchange; or
- the introduction of APD. If APD is already in use, a 'wet' day may have to be introduced.

It is often difficult to get patients to accept increases in their dialysis regime, which emphasises the importance of pushing the treatment to the limit of tolerance at the beginning of dialysis.

If all these measures fail, some patients will need to be transferred from CAPD to HD.

These minimal standards are lower than those recently recommended by an ad hoc committee on PD in the USA [Burkart and Villano 1997]. It may well be necessary to raise the British standards before our next edition if evidence that raising Kt/V or C_{cr} confers benefit accumulates in the interim.

■ ***Details of recommended methods for the estimation of Kt/V, weekly creatinine clearance and nitrogen appearance rate (protein catabolic rate (PCR)) are given in Appendix 4.***

Outpatient monitoring of patients during CAPD

6.27 This should include:

- Assessment of weekly *Kt/V* and/or creatinine clearance (6.26)
- Annual PET measurement, or as indicated clinically (6.16)
- Reassessment of prescription in the event of excessive weight gain
- Collection of biochemical data (6.12–6.15)
- Assessment of residual renal function annually and as clinically indicated

Residual renal function

6.28 As emphasised above, decline in residual renal function has an important bearing on the adequacy of dialysis. Consequently, residual renal function should be assessed at least annually as part of the assessment of total adequacy, or whenever underdialysis is suspected [Tattersall *et al* 1993]. The urine collection can also be used to measure urea nitrogen appearance, from which can be calculated the PCR. In steady state, this correlates approximately with dietary protein intake, which should be at least 1.0 g/kg/day. Details of recommended methods for measurement of residual renal function are given in Appendix 4.

6.29 A significant correlation between *Kt/V* and PCR is partly a mathematical artefact of the use of *V* to calculate both parameters [Harty *et al* 1993, 1994]; it should not be used to assess the impact of adequacy of dialysis on nutrition.

Recommendation

In patients with urine output, residual renal function should be measured at least annually. **(B)**

Peritonitis

6.30 Peritonitis is the major and most serious complication of CAPD. Apart from the immediate deleterious effects and distress of the acute episode, there is mounting evidence that repeated attacks of peritonitis are associated with earlier failure of the peritoneal membrane. How the frequency of episodes of peritonitis should be measured and expressed remains a subject of controversy. In some studies, episodes within a short and variable period of either catheter insertion or beginning dialysis are excluded, and in other studies included. In general an *actuarial analysis of time free of peritonitis* is the best way to express the peritonitis rate [Maiorca *et al* 1983; Port *et al* 1992], and we advocate its use, but this has been little used in clinical practice. Despite its theoretical and practical disadvantages, the number of episodes/unit time remains in widest use, and the recommendation below is couched in these terms.

6.31 Peritonitis rates are improving with the introduction of disconnect systems [Maiorca *et al* 1983; Churchill *et al* 1989]. The successful diagnosis and management of peritonitis requires high quality microbiological facilities and close liaison with

the microbiology department. Protocols for managing peritonitis episodes have been published [British Society for Antimicrobial Chemotherapy 1987; Keane *et al* 1993, 1996], but it must be noted that the use of vancomycin as a first-line 'blind' antibiotic has been curtailed recently because of the emergence of vancomycin resistant organisms [Golper and Tranaeus 1996], and alternative regimens have not been evaluated so extensively [Keane *et al* 1996].

Recommended minimum standard using the disconnect system

Peritonitis rates should be <1 episode/18 patient-months. (**A**)

The negative peritoneal fluid culture rate in patients with clinical peritonitis should be less than 10%. (**A**)

The initial cure rate of peritonitis should be more than 80% (without necessity to remove the catheter). (**A**)

■ ***Suggested methods for the culture of PD fluid are described in Appendix 4 (A4.2).***

Peritoneal access

6.32 Guidelines for insertion of peritoneal access catheters and their subsequent care have been published by Gokal *et al* [1993]; we advocate the use of these.

Outcome measures and audit

6.33 Outcome measures of patients and technique survival are functions of case-mix, availability of appropriate dialysis facilities and patient related factors such as age and comorbidity. Survival data for patients on PD are in general similar to those for HD [Brunner *et al* 1988; Geerlings *et al* 1994; Nolph 1996]. As for patients receiving HD, survival is influenced greatly by age and comorbidity, especially diabetes mellitus and cardiovascular disease, as discussed in Appendix 4. Overall national and international survival data are available from the register of the European Renal Association [Brunner *et al* 1988], by age [Valderrábano *et al* 1995], and by comorbidity [Khan *et al* 1996].

Recommendation

Survival data should be audited by the UK Renal Registry. In the interim, the outcome results for UK patients from the register of the European Renal Association should be used for setting standards and comparative audit, and are included at the end of Appendix 3 (A3.8).

■ ***A list of suggested audit items for patients on peritoneal dialysis is included in Appendix 3 (A3.2)***

7 Transplantation

Access to transplantation

Demand exceeds supply

7.1 Renal transplantation is at the moment the most economical, successful and hence cost effective treatment for patients with end stage renal failure (ESRF). The supply of donor organs, which averages only 30/million population per year in the United Kingdom, is greatly outstripped by demand, which is a minimum of 48/million population/year [United Kingdom Transplant Service Special Authority (UKTSSA) 1989, 1995a], depending upon criteria for selection for this form of treatment (see 7.3–7.5). This gap cannot be closed by using only cadaver kidneys for transplantation [New *et al* 1994; British Transplantation Society 1996]. Donor organs are thus an extremely valuable resource which must be used optimally. However, it is important also that equity of access to transplantation be achieved, both in geographical terms and for those with uncommon HLA tissue types. The dilemma remains that these two goals are in conflict.

Who should be transplanted?

7.2 Not all patients receiving dialysis are suitable for transplantation (see Chapter 4). There is evidence [McMillan and Briggs 1995] that selection criteria for placing on the active list for transplantation vary widely throughout the United Kingdom; the proportion of patients maintained on dialysis who are registered with the UKTSSA for renal transplantation varies from 20% in some units to 70% or more. In addition, some units put patients 'on call' who have yet to reach a requirement for dialysis, and these patients receive 'pre-emptive' transplants, competing for kidneys with those already on dialysis, in some cases for many years. This diversity of policy has the disadvantage that it leads to inequity in the distribution of organs, even though it may benefit individual patients.

Suitability for transplantation

7.3 In the United States, practice guidelines have been formulated on the basis of consensus and literature review [Kasiske *et al* 1995]. In the United Kingdom, however, definitive criteria for acceptance on to transplant waiting lists have yet to be agreed, although diabetes, vascular disease and a history of malignant disease are major comorbid factors that reduce the likelihood of acceptance in many units (see end of Appendix 4). This attitude is based on poorer survival of such recipients, and hence of the transplanted kidney (death with a functioning graft).

7.4 Although at the moment we cannot recommend standards for investigation of potential transplant recipients, it is essential that appropriate data be collected by pre-transplant investigation to allow definitive criteria to be applied in the future. This applies particularly to cardiovascular disease. Kasiske *et al* [1995] outline the case for investigation of the cardiovascular system in potential transplant recipients and suggest investigative protocols.

7.5 Chronological age of itself (at least up to 65–70 years) has been shown in a number of studies not to be a major factor in determining the short term (<5 years)

survival of grafts [Cameron *et al* 1994; Cantarovich *et al* 1994; Tesi *et al* 1994] because an increase in deaths with a functioning graft is counterbalanced by a lower rejection rate in the elderly. However, it is obvious that the outlook for older recipients must be poorer in the long term (>5 years). To deal with these uncertainties, meetings between transplant staff and dialysis staff need to be held to review patients aged over 55 years annually and those aged over 65 years 6-monthly, because changes in suitability for transplantation may take place. Patients should be placed on, or removed from, transplant waiting lists only after discussion and with the agreement of nephrologists, transplant surgeons and the patients themselves, and recorded in the notes.

Recommendation

There must be demonstrable equity of access to donor organs irrespective of gender, race or district of residence. Age of itself is not a contraindication to transplantation but age related morbidity is important. All patients on dialysis should be considered formally by physicians and surgeons for transplantation, or for exclusion from the transplant waiting list. Their cardiovascular and other comorbidity should be assessed and recorded as outlined in Appendix 4 (A4.7). Assessment should be repeated at least annually.

How should kidneys be allocated?

7.6 Debate continues on the practical [Chang 1996; Starzl and Fung 1996] and ethical [Guttmann 1996] basis for allocation of kidneys. Ten years ago in the United States the United Network for Organ Sharing (UNOS) introduced a formal system of allocating points to potential recipients on a standard scoring system, using such criteria as time waiting for a graft, medical urgency, tissue matching and anti-HLA antibody status. In practice, however, tissue matching has come to be the dominant criterion. In the UK the system remains very much an *ad hoc* one, varying from region to region in its design and operation. The issue remains crucial but unresolved, and in this document we make recommendations only on the level of tissue matching to be aimed for. This does not mean, however, that it is the only factor that should be taken into consideration in allocating organs.

Organ donation rate

Cadaver organ supply

7.7 The total kidney donation rate (cadaver and living donors) in the UK, at 30/ million population/year, is exceeded consistently by that in some major European countries such as Austria and Spain [Matesanz *et al* 1994, 1996; British Transplantation Society 1996], and data are available to suggest that the supply of organs could be increased nationally by approximately 20% [Gore *et al* 1992]. The topic has been discussed extensively in a report of the British Transplantation Society working party [1996], which is in turn discussed by Wight and Cohen [1996], as well as by the King's Fund report [New *et al* 1994]. Organ supply is clearly central to expansion of transplantation, the best and most efficient treatment for renal failure. Many topics remain controversial, for example standards for organs to be retrieved, methods of organ preservation and the use of non-heart-beating donors. (Microbiological aspects of organ donation are discussed in Chapter 11.)

7.8 Cooperative networks of intensive care units in the hospitals served by the transplant and dialysis units should be developed using transplant coordinators, and sustained by educational systems. Currently these services are inadequate and

underfunded [Falvey and Morgan 1996], and the costs associated with their expansion and improvement, together with formal recognition, will need to be met. Liaison with and involvement of intensivists and their staff is crucial.

7.9 At the moment, the cost of organ retrieval of all types is borne disproportionately by renal transplant units, since retrieval was initially funded largely through this channel. This point needs to be included when costing renal services, and taken into consideration by purchasers when constructing future budgets for transplantation of kidney and other organs. Review of coordination structures for multiple organ donation is needed.

Living donor transplants

7.10 Even a much improved cadaver organ donation rate is unlikely to satisfy the demand, and therefore the need continues for donation by living donors. In Norway, 40% (17/million population/year) of all kidneys are obtained from living donors, so a total rate of more than 40 transplants/million/year has been achieved [New *et al* 1994]. An important additional justification for living donor transplantation is its superior success rate in comparison with cadaver transplantation. A living organ donation programme requires great care to ensure that donation is altruistic, without coercion or reward, that the risks to the donor are minimised, and that the requirements of the Human Organ Transplantation Act [1989] are met in all respects. Clearly defined protocols of investigation and management are essential, and such transplants should not be carried out where they constitute an occasional event. Guidelines for evaluation of living kidney donors have been drawn up by an *ad hoc* subcommittee of the American Society of Transplant Physicians [Kasiske *et al* 1996]

7.11 The use of motivated but unrelated living donors, such as spouses, unmarried lifelong partners, step-parents or even close friends, remains controversial, although now the results obtained approach those with related living donors and are often superior to those obtained using cadaver grafts [Terasaki *et al* 1995]. It is likely that the numbers of this type of graft will increase; the provisions of the Human Organ Transplantation Act are specifically designed to prevent abuse in this area.

Recommendation

Services for kidney retrieval must be an integral part of organ transplant services, and costed into them. Purchasers should fund efforts to increase the number of cadaver organs made available, by the setting up of transplant coordination and organ procurement teams, to ensure that adequate educational programmes are in place; an important aspect of this is improved communication with intensive care units. Thought should be given to ways whereby an ethical expansion of the proportion of living donor organ transplants may be achieved.

The transplant unit

Site

7.12 Renal transplantation facilities should be centralised, taking into account geography, population density and communications. This avoids duplication of specialised resources such as histocompatibility laboratories and organ retrieval teams, and permits training of medical and other staff.

Ward facilities

7.13 The transplant unit should have 6 dedicated beds per million population (pmp) served for new transplants, one-third of which must be single-bed cubicles. This figure may need to be varied in the light of geography, communication networks and population density. Dialysis, as needed, should be possible at all stations. Beds must be within a single ward to ensure high standards of training, nursing and cross-infection care (see Chapter 11), though all the beds in the ward need not be devoted to transplantation.

Support services

7.14 Full support is essential, including access to operating theatres 24 hours a day, to allow prompt transplantation of incoming cadaveric kidneys, to minimise the cold ischaemic time [Cecka *et al* 1992; Connolly *et al* 1996]. Elective operating theatre facilities will also be needed. Laboratory support is essential, including histocompatibility and antibody testing (see Appendix 4). A full haematology and biochemistry service is needed, including blood grouping and provision, where necessary, of cytomegalovirus (CMV) negative blood. Pharmacological assays will also be needed for immunosuppressive and some other drugs. There must be immediate and continuous access to virology and bacteriology services, including screening for CMV antibody and antigen (PCR), HIV, hepatitis B and C (see Chapter 11), and histopathology services with a specialist histopathologist trained in the interpretation of renal transplant biopsies.

Imaging

7.15 Facilities to which access is essential are routine X-ray, conventional ultrasound plus Duplex ultrasound for vascular imaging, computed tomography (CT) and radioisotope scanning, angiography and the services of an interventional radiologist. Magnetic resonance imaging (MRI) is not essential at the moment, but access will be needed for a few patients. It is important to emphasise that these services will often be required at short notice and out of normal working hours.

Other medical and surgical disciplines

7.16 Access to urology services and advice is necessary. Since vascular disease is common both in prospective recipients and after transplantation, the transplant unit needs access to full clinical and investigational cardiological assessment, including coronary angiography and thallium dipyridamole scanning. Joint management of diabetic patients with a diabetologist is desirable before and after transplantation. Access to other specialties such as neurology, gastroenterology, thoracic medicine and infectious disease will be needed on occasion for acute consultation. Long term morbidity in transplant recipients involves a high incidence of skin lesions, some of them malignant, and the advice of a dermatologist will be needed on a regular basis.

Clinics

7.17 Patients should be followed in the transplant centre for at least 3 months following transplantation. Consultant led clinics will be needed for this, although junior staff should participate under supervision, as may nurse practitioners. The number of patients attending the transplant clinic will depend upon the number of transplants performed, the success rate, and the policy with regard to discharge back to local nephrologists/physicians. All recipients should be reviewed at least annually at the transplant centre unless the facilities in the dialysis units served, and the ability to transfer data centrally, make this unnecessary (see 7.19).

7.18 *Living donors* should be followed also on an annual basis, since they have a

higher incidence of proteinuria and hypertension than control populations. Renal function should be assessed at each visit. Donors may also need counselling, especially if the transplant has been a failure, and this should be available.

Data storage and access

7.19 This is essential for both clinical and service audit; both staff and equipment must be costed into the service, as discussed in the section on dialysis. The database should be interfaced with the UKTSSA which is integrated with the National Renal Registry. If patients are referred back for continuing care to local nephrologists, the local databases must be linked to the transplant unit.

Staffing

7.20 It would not be appropriate in this document to go into staffing in detail; the topic, including nursing requirements, has been dealt with in the *Review of renal services in England* [Department of Health 1996a]; its patient database is being updated at the time of writing. However, there should be at least 4 surgeons trained in transplantation per 2 million population, plus appropriate support staff; consultant rotas should not be more than 1:4 [Royal Surgical Colleges 1997]. Cross-cover by surgeons untrained in transplantation is undesirable and, where such rotas exist, should be phased out by alliances with adjacent units by negotiation between Trusts. The presence of only a single-handed consultant transplant surgeon is to be condemned.

Integration with transplantation of other organs

7.21 Multiple organ donation continues to increase, and organ retrieval services must be designed with this in mind. A number of diabetic patients will have kidney-pancreas transplants, and these will in general be managed within transplant units but with input from diabetic specialists. Occasionally, recipients will receive kidney-liver and kidney-heart transplants, and the site of their management may vary. The services for these patients must be sited and administered with care, and joint management in transplant centres performing multiple transplants is desirable.

Recommendation

Transplant units should in general serve at least 2 million total population, depending upon geography, communications and population density. They must be appropriately located, and perform at least 50 transplants per year except where geography dictates the need for a smaller unit. **(C)**

Transplant units must be adequately staffed both medically and surgically, with training opportunities for junior staff, and have full support services. Full integration with dialysis services and regular contact with physicians in joint care of transplant patients is essential. **(C)**

Histo-compatibility matching and allocation of donor kidneys

7.22 The tissue typing laboratory should be directed by a medical consultant or consultant clinical scientist who is in charge of the day-to-day laboratory activity and is available for contact outside normal working hours. The laboratory must meet Clinical Pathology Accreditation (UK) Ltd standards, must participate in the UK National External Quality Assessment (NEQAS) for histocompatibility and immunogenetics, and must be actively involved in research and development. Staff providing on-call services must be trained to at least the British Society of Histocompatibility and

Laboratory standards

Immunogenetics (BSHI) Certificate of Competence level, whilst senior staff should possess the DipRCPath and the director MRCPath or FRCPath.

7.23 *Technical developments* in laboratory aspects of kidney transplantation have been dramatic and are likely to continue. The advent of molecular biological techniques has had a significant impact on the quality of HLA matching, and interpretation of crossmatch results from various techniques has enabled many patients to receive a successful transplant. The BSHI has established standard descriptions of currently available techniques which clinicians should adopt when requesting tests (see Appendix 4).

7.24 The regulations incorporated in the Human Organ Transplantation Act [1989] specify that, in living donor transplantation, tissue typing tests are to be carried out by an '*approved tester*', appointed by the Department of Health, to establish a claimed genetic relationship. When there is no claimed genetic relationship or when such a relationship cannot be established, the case must be referred to the Unrelated Live Transplant Regulatory Authority (ULTRA) via the ULTRA Secretariat at the Department of Health.

7.25 *Approved testers* must be fully aware of their responsibilities under the regulations, including receipt of signed statements claiming a relationship, documented blood samples, completion of specified tests, recording and long term storage of test results and formal reporting. Testers must be aware of the limitations of the specified tests and should report accordingly. The penalties defined in the Act should be understood.

Recommended standard

An efficient, high quality tissue typing service must be seen as an essential part of a successful kidney transplant programme.

Cadaver kidneys must be allocated on the basis of matching for HLA alloantigens and crossmatching supported by efficient antibody screening. **(A)**

Living donor kidneys and recipients must be typed by an 'approved tester' appointed by the Department of Health.

The tissue typing laboratory staff must be an integral part of the transplant team.

Tissue matching in transplantation

7.26 Identity or compatibility of ABO blood groups between donor and recipient currently is essential. The principle of matching the donor kidney tissue type (HLA- or allo-antigens) to that of the recipient to optimise transplant outcome and minimise rejection is well established and has been practised by UK units since 1978. Matching is especially important in determining longer term (5–15 years) outcomes [Opelz *et al* 1992; Held *et al* 1994].

7.27 A system for mutual exchange of donated kidneys based on HLA matching is operated by the UKTSSA; currently (1997) a working group is seeking to revise and improve its mode of operation. All UK transplant units are encouraged to join the national scheme and register their potential recipients. The numbers of donor kid-

neys retrieved that are exported to other units, and those received from elsewhere, are recorded for each participating unit and openly monitored.

Beneficial matching

7.28 A 'beneficial' match is defined as *no mismatches for HLA-DR with a maximum of one mismatch at either of HLA-A or -B. (A:B:DR 000 or 100 or 010*). Analyses by the UKTSSA have shown superior graft survival of beneficially matched kidneys, but no effect of matching between the various other grades of mismatch [Gore *et al* 1988; Gilks *et al* 1990; Rogers *et al* 1996]. In the UK about 30% of cases are 'beneficially' matched, and the remainder are allocated to recipients on the basis of a number of factors, including a minimum HLA match, time on the waiting list and, in some units, the relationship between donor and recipient ages. Thus a major aim is to restrict total mismatches. Patients with high levels of antibodies specific for previously mismatched HLA alloantigens can join the 'acceptable mismatch' scheme which aims to provide donor kidneys to patients for whom matching and crossmatching are difficult.

7.29 Each transplant unit retains the option of participating or not in the national exchange scheme, bearing in mind that figures for input and retrieval figures for kidneys are published for individual units. Overruling factors such as clinical urgency are accommodated, though the need for highly urgent kidney transplants is no longer recognised by the existence of a nationally based list of such patients.

7.30 Mismatches for common HLA antigens should be avoided wherever possible in young recipients, who may thus acquire HLA-specific antibodies against a high proportion of potential donors, and make re-transplantation difficult should their graft fail.

Recommended standard

Beneficial matching of donor kidneys should be achieved in a minimum of 30% of recipients. **(A)**

Crossmatching

7.31 Immediate, 'hyperacute' rejection of transplanted kidneys can be prevented by performing a crossmatch between recipient serum and donor lymphocytes. Since 1965 the techniques available to detect interaction of recipient antibody and donor target antigen and the interpretation of crossmatch results have been greatly extended. There are many different techniques used in different centres (see Appendix 4), and different policies on how the outcome of the crossmatch is used. Each centre should establish its own policy based on published data and local experience, but a crossmatch must always be performed prior to kidney transplantation.

7.32 The value of crossmatching by flow cytometry (FC) has become apparent recently, particularly in recipients at high risk of rejection such as children and patients with high levels of circulating antibody or previous transplantation, but careful standardisation and quantification of the results are necessary [Harmer *et al* 1996; Mahoney *et al* 1996].

Recommended standard

All donor-recipient pairs should be crossmatched by an acceptable technique before transplantation. FC crossmatching should be available for re-transplants, children and highly sensitised recipients (7.35–7.37). **(B)**

Screening for antibodies in recipients

7.33 Efficient HLA matching and crossmatching procedures should be used with a screening programme to detect HLA-specific antibodies. *Sensitised patients* are those who have been exposed to HLA (allo-)antigen through pregnancy, blood transfusion or a previous transplant, and who may have HLA-specific antibodies detectable in their serum. Blood group antigens other than ABO rarely give problems, with the exception of the Lewis (Lew) group.

7.34 The definition of sensitisation depends crucially upon the techniques used. The assay most widely used is the *complement dependent cytotoxicity assay* using lymphocytes as the target cells. A cell panel of at least 20 cells from different donors may be sufficient to cover most HLA specificities, but most laboratories use larger numbers (50–75) of test donors. The panel must be carefully selected to contain HLA specificities (HLA-A, -B, -Cw, -DR, -DQ) occurring in combinations that allow efficient interpretation of results. Although the degree of reactivity to the panel is often expressed as a percentage, this is misleading since the panel is chosen to represent a wide range of antigens and not the population as a whole. Recently, tests based on ELISA (enzyme-linked immunosorbent assay) and FC have become available, with benefits of increased sensitivity and specificity. Assays used to detect allosensitisation must have a sensitivity equivalent to crossmatching techniques.

Recommendation

All screening for HLA-specific antibodies should use a typed panel of donor cells which allow interpretation of positive reactions.

All potential transplant recipients should be screened for HLA-specific antibodies 2 weeks after any blood transfusion. **(B)**

All potential recipients should be screened at least 4 times a year for HLA-specific antibodies. **(C)**

The tissue type of fathers of children borne by female potential recipients should be determined wherever possible.

Highly sensitised recipients

7.35 Conventionally, *highly sensitised patients* (HSPs) are defined as those who react with more than 85% of panel cells, despite the caveat in section 7.34. To qualify as an HSP, the potential recipient must be shown to have IgG antibodies specific for alloantigens, most often for several HLA-A, -B or -Cw specificities, usually those common in the donor population. *Autoreactive IgM antibodies* may give the impression of high panel reactivity, but since these antibodies do not prevent successful transplantation their presence must be carefully defined. However, recent evidence suggests that IgM HLA-specific antibodies *do* occur, and may be deleterious, so simple *in vitro* destruction of IgM antibodies *before* testing is not recommended.

7.36 Evidence of sensitisation in the form of circulating antibodies varies with time, so serum samples must be taken within 2 weeks of any blood transfusion, in the immediate post-transplant period, and in all patients on the transplant waiting list at least quarterly. Ideally, the HLA phenotypes of the father(s) of all past pregnancies should be available. All HLA specificities against which the potential recipient may react should be recorded as '*unacceptable antigens*', and should be avoided in the transplant kidney.

7.37 Some HSPs can be shown not to react with certain specificities; these should be recorded as '*acceptable mismatches*'. Survival of HLA *mis*matched kidneys in HSPs is generally poor, whereas well matched kidneys survive well, and therefore 'beneficially' matched kidneys should usually be allocated. HSPs are high risk recipients, and so *should* receive optimum transplants.

Recommendation

Highly sensitised recipients should have their serum screened for HLA-specific antibodies, the specificities of which should be defined carefully. They should receive kidneys that bear only matched antigens (or 'acceptable' mismatches). (**B**)

After transplantation

7.38 If antibody screening is carried out regularly after transplantation, accurate crossmatching for re-transplantation can help achieve success rates after re-transplantation as good as those for first transplants.

Recommendation

Following transplantation it is essential that the tissue typing laboratory continues to receive serum samples for antibody screening at each clinic visit. (**C**)

Interaction between laboratory and clinicians

7.39 Transplantation is a multidisciplinary clinical service and the best success rates can be achieved only through close liaison of laboratory and clinical staff. Highly trained and dedicated staff in a histocompatibility laboratory must meet with clinical colleagues regularly and must provide a 365 day, 24 hour service.

Immunosuppressive regimens

7.40 At the moment there are insufficient data to permit specific recommendations on immunosuppressive regimens of monotherapy, double or triple therapy using prednisolone, azathioprine, cyclosporin microemulsion (Neoral^{TM}), tacrolimus (FK 506) or mycophenolate mofetil. Nor is the role of protein immunosuppressants (antilymphocyte globulin, OKT3 etc) clear. At the moment the most commonly used regimen for the first year after transplantation is triple therapy with prednisolone, azathioprine and cyclosporin, but it is likely that mycophenolate mofetil and/or tacrolimus will become increasingly used during the next few years because the number of early rejections under regimens using these drugs appears to be lower, and lower rates of early rejection in turn are correlated with better long term function and graft survival.

7.41 Graft survival and incidence of rejections appear to be similar with regimens in wide current use, except that graft survival is lower and rejection more common with regimens containing only prednisolone and azathioprine compared with those containing cyclosporin [Opelz *et al* 1995], and newer agents. However, morbidity (eg infection and skin cancers) may well differ and early rejection rates be lower with the newer drugs (mycophenolate mofetil and tacrolimus). It is likely that a greater diversity of regimens will be used in future to 'tailor' therapy more accurately to individual patients' needs.

7.42 New agents such as mycophenolate and tacrolimus are under trial, and only further controlled studies will allow any recommendations to be made. Until these are completed, outcomes need careful auditing to allow accumulation of informative data. The choice of immunosuppressive regimen has substantial cost implications, which will need discussion with purchasers, but the high costs of a failed graft must be borne in mind also; cost effectiveness data are needed urgently in this area.

Clinical outcomes and audit

7.43 Clinical and medical audit should be an integral part of the work of the transplant unit. Patient survival, morbidity and transplant outcomes depend critically upon a number of case-mix factors such as the age and comorbidity of the population transplanted (see Appendix 4). This in turn depends upon the criteria for the selection process applied locally first for selecting those on dialysis as potential transplant recipients, and more remotely on the criteria for acceptance on to dialysis itself.

Recommended standard

A list of items that should be regularly audited before and after transplantation is included in Appendix 3 (A3.3).

All the data should be entered into the UKTSSA database in Bristol, so that they can contribute to, and be compared with, national and international data.

Standards of outcome in transplantation

7.44 Data for outcomes of transplantation in the United Kingdom for 1984–93 are available in the renal transplant audit document published by the UKTSSA [1995b]. At the moment recommended standards can be set for only some of the audit points for transplantation that are listed in Appendix 3, for patients without major comorbidity and whose ages lie between 15 and 50 years of age. The figures suggested below are minimum acceptable results for cadaveric transplantation; clearly, if every unit in the United Kingdom were to achieve something near the present mean or better, the average standard would rise considerably.

Organ retrieval rate

7.45 In 1992–3 the mean cadaver organ donor rate in the UK was 15 donors per million per year.

Recommended standard

At least 15 donors/million population/year should be retrieved.

Number of cadaver transplants

7.46 The mean figure in the UK in 1992–3 was 28 cadaver donor kidneys pmp.

Recommended standard

Each transplant unit should transplant at least 28 patients/million population/year with cadaver kidneys.

Cold ischaemic times

7.47 Lengthy cold ischaemic times (>30 h) are associated with inferior graft survival in some studies [Cecka *et al* 1992], and this is supported by unpublished data from the UKTSSA and Eurotransplant databases.

Recommended standard

Efforts should be made to limit the cold ischaemic time to less than 30 hours in all cases. (**B**)

Number of live donor transplants

7.48 The UK mean is 2 pmp per year, whilst in several European countries it is more than 5 and in Norway exceeds 17 pmp.

Recommended standard

Each transplant unit should transplant a minimum of 2 living donor grafts pmp/year, but it is hoped that a higher standard than this can be set in the near future.

Waiting time on transplant list

7.49 The median waiting time in the UK is 500 days, but differs markedly for sensitised and unsensitised patients, and is affected also by age, previous grafting and blood group. Of patients on the UK transplant waiting list 13.5% have been waiting more than 5 years, and 18% of these patients are not sensitised.

Recommended standard

Not more than 2% of non-sensitised patients should wait more than 5 years for a graft.

Selection for transplantation

7.50 Policies vary from unit to unit as to which patients, and what proportion, are placed on transplant call but the UK mean is 30%. Naturally there will be variation according to the case-mix of patients on dialysis, and particularly their comorbidity and age. In this area, equity and optimum use of the scarce resources of transplantable kidneys are in conflict.

Recommended standard

At least 30% of dialysis patients in any unit should be on the transplant waiting list. As recommended above (7.5), there should be regular review of the on-call transplant list.

Beneficial matching

7.51 Currently only 25% of recipients in the UK receive a beneficial match (see 7.28 for definition).

Recommended standard

At least 30% of recipients should receive a beneficial major histocompatibility complex (MHC) matched kidney. (**B**)

Time of onset of renal function

7.52 The mean rate of achieving immediate renal function in the UK is 68%, and is dependent upon the types of kidney accepted for use, and their handling within the transplant unit. It is known that kidneys with immediate function do better in the long term. In the UK 5% of kidneys never function.

Recommended standard

At least 70% of heart beating cadaver transplants should function immediately, and at least 95% should function eventually. (**B**)

Patient survival in cadaver transplants

7.53 The following are overall figures for the UK for first cadaver transplants performed from 1984 to 1993 and the recommended standards.

Recommended standard

Survival time of patient	Mean UK survival (%)	**Recommended minimum mean survival (%)**	
1 year	92	>90	
5 years	80	>80	
10 years	63	>60	(**B**)

It should be remembered that, unlike the outcome data given for all patients entering ESRF programmes in the UK given in Appendix 3 (A3.8), these data include patients of all ages, and diabetics. However, the age profile of transplanted patients resembles closely that of the data analysed in Appendix 3.

Graft survival in cadaver transplants

7.54 The following are overall figures for the UK for first cadaver transplants performed from 1984 to 1993 and the recommended standards.

Recommended standard

Survival time of graft*	Mean UK survival (%)	**Recommended minimum mean survival (%)**	
1 year	87	>80	
5 years	64	>60	
10 years	46	>45	(**B**)

** Including a graft in a recipient who dies with a functioning kidney and is 'lost to follow-up'.*

Second and subsequent grafts

Recommended standard

Graft survival of second grafts should be the same as for first grafts, provided that adequate analysis of alloantibodies and FC crossmatching are used (see Appendix 4). (**B**)

Patient survival with living donor

Recommended standard

There should be at least 95% survival at 1 year after grafting. (**B**)

Graft survival with living donor

Recommended standard

More than 90% of grafts should still be working at 1 year. (**B**)

Patients with comorbid conditions

It will remain much more difficult to set targets for transplant recipients with diabetes mellitus and/or significant comorbidity until some standard way of describing this and assessing the risk has been achieved. A suggested standard which can be used in collecting data is given in Appendix 4 (A4.7); in the future it should be possible to set standards for these patients.

8 Acute potentially reversible renal failure

Definitions

8.1 Acute renal failure (ARF) [Doherty 1998] is the condition in which a patient, usually with no known previous renal impairment, develops acutely failing renal function, with an increase, more or less rapid, of urea, creatinine, hydrogen ion, potassium and other renally excreted substances in the blood over hours or days. There are many causes of this condition, which may very simply be broken down into:

- *Medical conditions* (reaction to drugs, gross electrolyte disturbance, glomerulonephritis, infection etc). *Renovascular disease* has become increasingly recognised as a common cause of renal failure, particularly in the elderly and above all in patients receiving angiotensin-converting enzyme inhibitors. *Renal atheroembolism* has also been noted with increasing frequency.
- Multiple trauma such as industrial or road accidents or burns, civil or military violence etc.
- *Surgical interventions*, especially when complicated by *sepsis*.
- *Obstetric accidents*, which are rare in developed countries; it must be noted however that the few cases that still occur are often severely ill.
- *Obstruction of the urinary tract*, often acutely on a background of more chronic obstruction.

8.2 Recovery of renal function can be expected in the majority of patients with ARF from causes listed above, within a few days to a few weeks, but only if the patient survives the many vicissitudes of ARF and is aged less than 50 years. In some medical conditions, and in patients over 50 years of age, an increasing proportion have some preceding renal functional impairment in excess of that expected for age. These patients may fail to recover function or recover very limited function, such that they require long term dialysis, or only achieve partial recovery, though able to stop dialysis treatment. The proportion of patients surviving but not achieving independence from dialysis appears to be increasing [Bhandari and Turney 1996] — 'acute irreversible renal failure' [Firth 1996].

Incidence

8.3 A conservative estimate of the number of patients with ARF is that 70/million population/year require dialysis for this condition [Feest *et al* 1993]. No good data exist for those who become uraemic and need a specialist opinion but do not require or do not receive dialysis; probably about another 130/million population/year fall into this group. There is in addition substantial under-referral of patients in ARF, as judged by hospital laboratory data [Feest *et al* 1993]. ARF becomes more common with age, the highest incidence being in 90 year olds, but the largest absolute numbers occur in late middle age and early old age.

8.4 Within any hospital catchment area the number of cases of ARF per year will vary with the presence of other specialist services, for example cardiothoracic surgery or oncology. The case-mix of patients has changed greatly during the past decades [Turney *et al* 1990], together with a notable rise in the average age of those referred (now 60–65 years). Some patients who present as acute emergencies with uraemia, and appear initially to have acute reversible renal failure, are subsequently found to have an acute deterioration of renal function superimposed on chronic irreversible renal failure, or chronic irreversible renal failure itself, and remain on dialysis after 90 days [Bhandari and Turney 1996].

Types of acute renal failure

8.5 Two types of ARF should be distinguished:

- *Isolated failure of the kidneys* alone. ARF in which the kidneys are the sole organ involved, other organ systems functioning normally, at least to begin with.
- *Multiple organ failure*. ARF as part of a severe illness, infection or trauma in which other organ function is compromised.

The case-mix in different districts will contain different proportions of these two types of renal failure, and will vary according to local clinical activity, eg the presence of a trauma unit, a bone marrow transplant unit, liver or cardiothoracic surgery service. Respiratory insufficiency is the most common associated organ failure, but up to four or five other organ systems may fail simultaneously.

Where should patients be managed?

8.6 This raises controversial issues, and will depend to some extent upon what high dependency unit (HDU) facilities are available on the renal ward. ARF affecting only the kidneys varies in severity, but can in the majority of cases be managed appropriately in renal wards, which usually have the facilities of an HDU. Some patients with mild respiratory impairment (eg from fluid overload, which can be corrected) can be managed on a renal ward with HDU facilities, by techniques such as continuous positive air pressure (CPAP). In general, however, patients with other organ failure besides the kidney should be managed in an intensive care unit (ICU).

8.7 If managed in the renal ward or unit, it is inappropriate for patients with ARF to be managed in the same setting as long term dialysis patients, which carries many disadvantages, eg a requirement that these acutely ill patients be dialysed according to schedule rather than according to need; a special area for those in ARF needs to be designated.

8.8 For *any* patient in ARF, full support services, including access to specialist interpretation of renal biopsies (see Chapter 10) and a variety of imaging techniques, microbiology etc, are needed.

8.9 By contrast, patients with *multiple organ failure* require multidisciplinary management within a suitably equipped and staffed ICU. This will often require transfer of the patient, which should be carried out in a timely fashion supervised by an experienced and properly equipped transfer team [American College of Critical

Care Medicine 1993] in accord with the recommendations of the report of the working group on guidelines on admission to and discharge from ICUs and HDUs [Intensive Care Society 1997].

Recommendation

Patients with failure of the kidneys and one or more other organs normally should be managed in a high dependency or intensive care unit. **(C)**

When should therapy begin?

8.10 There are no absolute rules as to when treatment for renal failure should begin, but it is better to begin treatment apparently too soon than too late. *Thus, when it is obvious that ARF is established, dialysis should be started before complications occur.*

8.11 A common practice is to start renal failure treatment when the blood urea exceeds 30–50 mmol/l, but this depends also upon the rate of rise and clinical setting. Indications for emergency treatment include hyperkalaemia (plasma K^+ >6.5 mmol/l), pulmonary oedema as a result of fluid overload, acidosis leading to circulatory compromise, and gross symptoms of general uraemia.

Management techniques and site

8.12 *ARF involving only the kidneys* can be managed by a variety of techniques on the renal ward. Regular intermittent haemodialysis (see Chapter 5) is the commonest mode of management, but continuous filtration techniques may be used, although they are not available on many renal wards on a 24-hour basis. Peritoneal dialysis is still used in the occasional patient whose tissue breakdown is not severe (non-catabolic).

Recommended standard

A full range of treatment modalities for ARF involving only the kidneys should be available in the renal ward or ARF treatment area. Facilities appropriate to a HDU should be available in addition.

8.13 ARF in the critically ill associated with multiple organ failure, or other organ failure, must of necessity be managed in an ICU. Dialysis and filtration as part of multiple organ support should be carried out using biocompatible membranes for the dialytic technique since controlled trials have demonstrated increased survival [Hakim *et al* 1994b; Schiffl *et al* 1994] even though the benefit of this approach has been challenged; see Firth [1996] and Jacobs [1997] for reviews.

8.14 Although increased survival has not been demonstrated compared with conventional haemodialysis [Jakob *et al* 1996], treatment will most often be by continuous haemofiltration using a veno-venous blood circuit and a blood pump, but other techniques may be used according to individual needs and local skills: pumpless arteriovenous haemofiltration or (in carefully selected patients, and in children — see Appendix 2) peritoneal dialysis. More details of these dialysis techniques can be found in Chapters 5 and 6, which deal also with safety aspects. The important

point is that access to a range of techniques, including intermittent and continuous therapy, should be available in the ICU for these complex and very ill patients.

Recommendation

Biocompatible (polyacrylamide, polysulphone) membranes should be used for renal replacement therapy of patients with ARF as part of multiple organ failure. Whilst pumped veno-venous continuous haemofiltration will most often be used, other modalities of treatment should be available in the ICU. (**A**)

Patient supervision

8.15 Management of patients in ARF is an exacting task, the more so if two, three or more organ systems are failing at the same time. In the United Kingdom in 1996 there were about 300 ICUs and HDUs, and only some 70 renal units. Continuous treatment for ARF is available in at least two-thirds of ICUs, and only 20% of nearly 2,000 patients with ARF studied nationwide in 1991 were transferred to a regional unit [Stevens and Rainford 1992].

8.16 Those in charge of the patients in ICUs in hospitals without an in-house physician/nephrologist should have had appropriate training and experience to allow them to manage such patients' medical, surgical, nutritional and pharmacological needs with skill and confidence, and have defined formal links to a local renal unit for advice on the telephone and a visit or visits from a nephrologist. ICUs that treat only a handful of such patients each year should not have to manage them unaided.

Recommendation

In hospitals with both a renal unit and an ICU, patients with multiple organ failure including ARF should be managed jointly by intensive care physicians and nephrologists. At an appropriate time, if they recover other organ functions, they may be able to transfer to the renal ward if necessary.

In hospitals with an ICU but no renal unit, if those units see more than about 20 patients with ARF per year, the intensive care medical staff, especially at consultant level, will need to have had training in the medical aspects of ARF. (**C**)

Units likely to see 10–15 or fewer patients with ARF per year should normally transfer such patients to an appropriate nearby ICU with renal back-up. (**C**)

All ICUs without in-house access to a renal unit should have formal links with their nearest renal unit for advice and consultation, and that advice and consultation should be sought for all critically ill patients one of whose components is renal failure. This commitment has workload and staff implications for renal units. (**C**)

Costs

8.17 Although it is not the primary purpose of this document to examine costs, it should be noted that the individual cost of patients with ARF, especially those with multiple organ failure, is high — estimates suggest £40–50,000 per survivor requiring intensive care admission in 1990 [Firth 1990]. However, unlike chronic

irreversible renal failure, in the great majority of younger patients there are no subsequent year costs, though as many as 15% of elderly patients may survive but fail to recover renal function [Bhandari and Turney 1996].

Outcome standards

8.18 These are difficult to set because the case-mix of patients may influence outcome, eg the presence of a very active oncology, bone marrow transplantation, cardiothoracic surgery or hepatology unit supplying the unit with patients. Age, perhaps surprisingly, has little effect in many series on outcome compared with other acute medical problems such as sepsis; see Novis *et al* [1994] for review.

8.19 Despite many attempts [Chang 1990; Fagon *et al* 1993; Knaus 1993; Atkinson *et al* 1994], no clinical or biochemical index has been developed so far that can predict *individual* outcome reliably enough to be useful, though repeated measurements with time may improve prediction [van Bommel *et al* 1995]. All such patients require treatment based upon their individual disease process, clinical condition and response to treatment.

Recommendation

Survival to discharge in patients with any type of ARF affecting the kidneys alone should be more than 90%. **(B)**

In patients with combined renal and respiratory failure (dialysed and ventilated) 40–50% should survive until discharge. **(B)**

At least 5–10% should survive until discharge if a third organ system fails and this state persists for more than 3 days. **(B)**

All patients whose kidneys fail in the course of multiple organ failure should have replacement therapy if other active treatment is to continue, although it may in some cases be appropriate to withdraw dialysis along with other support at a later date.

8.20 *Death* in the presence of ARF in patients below the age of about 50 years is rarely the direct result of the renal failure itself, but from some aspect of the circumstances leading to the multiple organ failure.

8.21 The survivors of ARF usually will have no need of further dialysis if aged less than 55 years. However, over this age an increasing proportion either fail to recover renal function and continue on dialysis past 90 days [Bhandari and Turney 1996] or have underlying renal disease (especially renovascular disease), so what appears at onset to be an episode of ARF turns out to be an acute presentation of end stage renal disease. These patients present not only major problems of clinical management and rehabilitation but extra costs which have not yet been accurately defined.

Patients not requiring dialysis

8.22 Referral or consultation on patients with electrolyte problems and acute uraemia who do not require dialysis forms a major part of the work of renal units, and has cost and personnel implications. For convenience, a blood urea over 30 mmol/l and/or plasma creatinine greater than 300 μmol/l should act as a definition of such patients, who respond with return of renal function towards normal with

management of electrolyte and other problems, eg urinary tract obstruction, which is particularly common in elderly men [Feest *et al* 1993].

Recommendation

The numbers of patients presenting in acute uraemia but not requiring dialysis should be recorded and audited.

Audit

8.23 A list of items for which data should be recorded to audit acute renal failure is included in Appendix 3 (A3.4).

9 Chronic renal failure (pre-dialysis)

Progressive renal insufficiency

9.1 Patients with progressive renal insufficiency need careful follow-up and monitoring in an attempt to slow progression of the renal failure when possible, to prevent complications and to prepare patients physically and mentally for the appropriate renal replacement therapy.

9.2 Early referral of such patients to a nephrologist with facilities for full assessment, including diagnostic imaging, specialised renal histopathology, dietetics and urology, is indicated but it is not always practised in the UK at present. As an approximate guide, any patient with a plasma creatinine in excess of 150 μmol/l or whose plasma creatinine is rising rapidly (>50 μmol/l in 1–2 weeks) should be referred for assessment. Some will turn out to have reversible or controllable causes of renal failure (eg urinary tract obstruction, renovascular disease or hypertension); their prompt identification and treatment has clear clinical and financial advantages.

9.3 Patients with greater degrees of renal failure (eg plasma creatinine >300 μmol/l) have a lower potential for reversal or amelioration of renal failure, but blood pressure control and diet have much to offer. There are advantages also in following these patients with progressive renal failure in a separate *low clearance clinic*, in which their renal failure is managed and they are educated about modes of renal replacement treatment that can be provided.

Recommended standard

All patients who appear to have progressive renal insufficiency and a plasma creatinine above 150 μmol/l and/or rapidly rising plasma creatinine concentrations should be referred to a nephrology service for assessment and follow-up. **(B)**

Blood pressure control

9.4 As control of systemic hypertension is so far the only intervention (other than treatment of the primary disease) that has been demonstrated in controlled trials to slow the progression of chronic renal failure (CRF) [Klahr *et al* 1994], optimal blood pressure control is essential. Angiotensin-converting enzyme (ACE) inhibitors have been shown in prospective controlled trials to slow the decline of renal function in patients with chronic renal insufficiency [Maschio 1995], especially diabetic patients [Lewis *et al* 1993]. The position with regard to other antihypertensive agents such as calcium channel blockers remains unclear, but the various treatments given in the Modification of Diet in Renal Disease (MDRD) study [Klahr *et al* 1994] suggest that this could be a general effect of hypotensive therapy and not specific to ACE inhibitors.

9.5 Because of all the problems associated with interpretation of hospital clinic blood pressures, and possible future need to measure blood pressure on dialysis, there are obvious advantages in teaching patients to take their own blood pressures and bring the results to the clinic. The standard method using a mercury manometer and auscultation over an artery can prove difficult, so methods with a direct read-out may be needed. It should be noted that the only such machine approved by the Blood Pressure Subcommittee of the British Cardiac Society (Chair: Dr E O'Brien) is an oscillotonometric method, using machines of the Omron^{TM} series.

Recommended standard

Target blood pressures for all patients should be:

Age <60 — BP <140/90 mmHg (Korotkoff V if auscultation is used)

Age >60 — BP <160/90 mmHg (Korotkoff V if auscultation is used)

For certain diabetic patients these figures may need to be lower. **(A)**

Diet and biochemical control

9.6 Optimal control of protein, calcium and phosphate intake, immunoreactive parathormone (iPTH) and metabolic acidosis is important and may have an impact on morbidity, and possibly on the progression of renal disease.

9.7 Each patient should be assessed by a renal dietitian at regular intervals to optimise mineral, protein, fat and total calorie intakes. Although symptomatic benefit can be achieved, the role of protein intake in determining rapidity of decline in renal function remains controversial, despite several prospective controlled trials [Locatelli *et al* 1991; Williams *et al* 1991; Klahr *et al* 1994; Levey *et al* 1996]; see Maschio [1995] and Pedrini *et al* [1996] for reviews. The input of dietetic nursing and medical time required to achieve any putative benefit must also be taken into consideration; at the moment few units in the UK practise dietary restriction of protein in patients with a glomerular filtration rate <25 ml/min (plasma creatinine approximately 350 μmol/l depending on age, sex and body size). This policy conflicts with the advice arising from the MDRD study in the United States [Klahr *et al* 1994; Levey *et al* 1996] and with meta-analyses of trials [Pedrini *et al* 1996].

9.8 Protein intake is, in any case, restricted spontaneously to approximately 0.6–0.7 g/kg/24 h by uraemic patients not receiving any dietary advice [Ikizler *et al* 1995], although the quality of the protein selected may not be optimal or the caloric intake adequate. An intake of 0.8–1.0 g protein/kg/24 h biased in favour of first class protein seems best until further evidence accumulates. If protein restriction is practised it *must* be supplemented with an adequate increase in energy intake (>35 g/kg ideal body weight/24 h), and supervised carefully by a trained renal dietitian. Thus at the moment no standards can be recommended in this contentious and very important area.

9.9 Very low protein diets (0.2–0.5 g/kg/24 h), although possibly effective in some well supervised patients with very low renal function [Klahr *et al* 1994], are poorly complied with in practice, may lead to negative nitrogen balance and hence to increased morbidity, and are not recommended.

9.10 Control of serum bicarbonate within normal levels is advocated below. This may involve the administration of doses of bicarbonate that result in volume expansion and hypertension. The 'trade off' of these two goals has to be assessed for each individual.

Recommendation

Target ranges for:

Serum calcium	2.2–2.7 mmol/l (corrected for serum albumin)	
Serum phosphate	0.8–1.5 mmol/l	
Bicarbonate	within local normal limits	**(B)**

9.11 The influence of lipid concentrations on the evolution of renal failure in humans is equivocal. At the moment we do not make any recommendations for desired concentrations of plasma cholesterol, beyond those that would be applied to a population of individuals not in renal failure. When further data have accumulated it should be possible to make recommendations in this area.

Bone disease

9.12 There is considerable controversy about the early management of bone disease in adult patients with CRF. Some maintain that vitamin D in the form of calcitriol or 1α-hydroxycholecalciferol should be started in small doses at a very early stage, when the plasma creatinine is only 250–300 μmol/l. Baker *et al* [1989] and Hamdy *et al* [1995] provide controlled evidence in favour of this; others use this drug much later in the course of the disease. The serum alkaline phosphatase is an insensitive index of bone disease in this setting, a normal level providing little information and a raised level suggesting that disease of some severity is already present. Thus the measurement of serum iPTH by an intact hormone assay is necessary. Some recommend that the serum parathormone concentrations should be maintained at normal or nearly normal levels throughout; others are less aggressive.

Recommendation

Serum alkaline phosphatase should be monitored at each visit and maintained within normal limits

Serum iPTH should be maintained at two, or at most three, times the upper limit of normal (130–210 pg/ml). **(A)**

Anaemia

9.13 As their renal failure worsens, patients become more and more anaemic. Despite a growing body of data demonstrating that the use of erythropoietin (EPO) significantly improves quality of life in patients with advanced renal failure before they go on to dialysis [Besarab *et al* 1995], including at least one prospective controlled trial [Revicki *et al* 1995], EPO has been little used in this group of patients in the United Kingdom probably because of its high cost.

9.14 At the moment we are unable to set standards for target haemoglobin concentrations in pre-dialysis renal failure, but the influence on timing of entry on to dialysis treatment, with all its associated costs, may be affected by the haemoglobin level. However, no cost effectiveness data are yet available.

Beginning regular dialysis

9.15 The great majority of patients reaching end stage renal failure will be treated by some form of dialysis in the first instance, although a minority may receive a renal transplant (especially from a living donor) without any prior dialysis. The optimum time to start dialysis for each patient remains controversial [Hakim and Lazarus 1995]. However, all are agreed that delay in reaching dialysis beyond readily acceptable indices leads to a higher early mortality [Jungers *et al* 1993; Hakim and Lazarus 1995; Khan *et al* 1995; Eadington 1996] and to higher per patient costs [Campbell *et al* 1989; Muirhead and Blyndal 1995]. Some of this late treatment remains the result of late referral to the renal unit [Ratcliffe *et al* 1984; Campbell *et al* 1989], and can only be addressed by education of community health professionals.

9.16 The problem remains of how to decide when dialysis should begin in patients already known and attending a low clearance clinic. Urea kinetic modelling may be of use in this context [Tattersall *et al* 1995] since plasma concentrations of urea and creatinine may mislead, especially in elderly and malnourished patients. The suggestion has been made that dialysis should be started at a point at which the weekly small solute removal (*Kt/V*) falls to that regarded as optimal for a patient on dialysis. This corresponds to a weekly *Kt/V* of about 2.2 and implies starting small amounts of dialysis at a level of native creatinine clearance of about 15 ml/min and gradually increasing this as residual renal function falls away. If implemented, such a policy of 'early start/gradual increment' would have major organisational and financial implications. At the moment no recommendations can be made in this important field until more data are available.

Audit

9.17 A list of items for which data should be collected on patients in chronic renal failure is included in Appendix 3 (A3.5)

10 General nephrology

Prevention

10.1 The early diagnosis and prompt treatment of a number of renal diseases (eg reflux nephropathy, diabetes mellitus and hypertensive nephropathy) may prevent renal failure (see Appendix 4), obviate the need for renal replacement therapy and reduce comorbidity in those requiring treatment for end stage renal failure, which in turn improves prognosis. Only encouragement of referral or joint management through communication with colleagues in general hospitals and family practice can achieve this.

10.2 Clear recommendations for referral of patients with symptoms or signs of possible renal disease have yet to be worked out, though the Scottish Intercollegiate Guidelines Network (SIGN) has published documents recommending management strategies for patients found to have proteinuria and/or haematuria [SIGN 1997a,b].

Recommendation

In addition to patients with major renal syndromes — chronic (repeated plasma creatinine >150 μmol/l) or acute renal failure, acute glomerulonephritis or a nephrotic syndrome, or recurrent renal stones — general practitioners and consultant general physicians or specialists in other areas of medicine should be encouraged to refer for nephrology assessment in the following clinical settings:

- Abnormalities on urinalysis (proteinuria, haematuria) and/or raised plasma creatinine (>150 μmol/l) concentrations without apparent cause, with or without clinical complaints
- Persistent microhaematuria even if renal function is normal, particularly if the patient is under 40–45 years of age or there is associated proteinuria and/or hypertension (Older patients with isolated haematuria of any dimension should be referred to a urological haematuria clinic)
- Frank haematuria in patients under 40–45 years of age
- Persistent proteinuria with normal renal function, especially if accompanied by haematuria
- Refractory hypertension associated with abnormal urinalysis and/or elevated plasma creatinine concentration
- Patients with known polycystic kidney disease, even if renal function is normal, and their close relatives should they require counselling
- Patients with urinary tract infections in some circumstances*
- Diabetics with clinically evident proteinuria, even with normal renal function
- Pregnant women with known renal disease **(B)**

** With hypertension; infection with unusual organisms (eg Proteus, Klebsiella); in adult males; during pregnancy. Patients with infections and symptoms of voiding dysfunction may be referred to either a renal or a urological clinic.*

Support services

10.3 Renal units must have access to a full range of support services, including all modes of imaging, histopathology (see 10.6), microbiology (see Chapter 11), social services, dietetic services and occupational therapy. Many services will be required on occasion outside normal working hours.

Liaison with colleagues

10.4 The nephrologist will need to cooperate on a daily basis with many colleagues, both in a consultative capacity for renal problems arising in patients under their care, and also in asking their help in specialist problems in patients with renal disease under their own care.

The nephrologist will be involved also in cooperating with community services, especially in the care of elderly patients with or without renal failure or on dialysis.

Recommendation

The care of the majority of patients with ongoing renal disease, especially those with renal failure (plasma creatinine >300–400 μmol/l), should be in a special low clearance clinic (see Chapter 9). (**B**)

Diabetes mellitus

10.5 The care of patients with diabetes mellitus presents particular problems of management, such as the care of the feet and eyes, but there is hope for prevention. There is evidence from a controlled trial that the degree of control of diabetes may postpone or prevent renal damage [Diabetes Control and Complications Trial 1993], but this must be maintained at a level very close to that at which hypoglycaemic episodes become common. There is evidence that the use of angiotensin-converting enzyme inhibitors may prevent diabetic nephropathy or slow its progression [Lewis *et al* 1993].

Recommendation

Care of patients with diabetes and renal disease, especially those with renal failure, should be through joint diabetic/renal specialist management. (**C**)

Systemic immunological disorders

10.6 The kidney may be involved in a variety of systemic immunological disorders such as vasculitis and systemic lupus erythematosus, sometimes at onset but also sometimes late in the disease, by which time the patient is already under observation and treatment. There is much advantage in liaison with colleagues likely to encounter such patients, especially rheumatologists, and in having joint clinics at which these patients can be reviewed.

Renal biopsy

10.7 Renal biopsy performance and interpretation is an important part of the practice of general nephrology. In terms of diagnostic and prognostic utility, where the biopsy is performed and who performs it are less important than who interprets it. At the moment we cannot suggest standards for the various methods of renal biopsy, including mechanical methods such as the Biopty™ gun.

Performance

10.8 In some hospitals, radiologists will perform the renal biopsies, but it is important that specialist registrars in nephrology receive instruction and practice in doing renal biopsies. Less experienced staff, such as senior house officers, should not normally be involved in performing biopsies.

Interpretation

10.9 Renal biopsy interpretation is a highly specialised component of histopathology. It should be performed only by, or under the supervision of, a specialist renal pathologist participating in appropriate audit, quality assurance and continuing medical education activities in pathology. In some renal units this will mean sending the biopsy specimen elsewhere for interpretation.

10.10 The laboratory should be accredited for histopathology and have on site facilities for electron microscopy and immunohistological staining of the biopsy specimens, which are essential for the interpretation of many specimens. Reporting times should be such that appropriate and timely intervention can be achieved clinically.

10.11 For quality control and medical education, regular joint clinico-pathological meetings should take place.

Recommendation

Interpretation of renal biopsies should take place in a suitably equipped and staffed specialist histopathology laboratory. This may mean sending the biopsy to another hospital for processing and assessment. (**B**)

Audit

10.12 There are few audit measures in general nephrology that permit evaluation of the service, other than general audit such as waiting times for, and in, outpatients or for ward admission, cancellation of interventions, lengths of hospital stay etc. We suggest points for audit of renal biopsy in Appendix 3 (A3.6).

11 Blood borne viruses and microbiology in dialysis and transplantation units

Microbiological services

11.1 All renal transplant and dialysis units require ready access to comprehensive microbiology; specific requirements for patient management are discussed in Chapters 5–7. This chapter deals mainly with aspects of cross-infection in and between patients and staff. It should be noted that results, especially those of tests for blood borne viruses (BBV), will be needed out of hours, and rapidly; this requires collaboration and discussion with local microbiologists.

Blood borne viruses

11.2 In 1972 the Rosenheim Advisory Group [Department of Health 1972] issued good practice guidelines to prevent the transmission of hepatitis B virus (HBV) in dialysis and transplantation units. New BBV, including particularly hepatitis C and human immunodeficiency virus (HIV), have been identified since then, but separate guidance has not been issued. Further BBV such as hepatitis G [Alter 1996; Masuko *et al* 1996; Schlaak *et al* 1996] have been identified; although their carriage rate is greater in patients on dialysis than in the general population, their clinical significance, especially in the long term, remains unclear.

11.3 Recognised 'universal precautions' against viral transmission, designed both for the protection of the staff and to prevent cross-infection between patients, are an essential discipline in dealing with dialysis patients. All patients with either chronic (CRF) or acute renal failure (ARF) should be managed as if they were chronic virus carriers until they have been fully tested. Regular testing is part of the subsequent management of patients and the running of renal units. Staff training should incorporate and emphasise precautions against BBV. Where available and effective, immunisation should be offered to staff; there is evidence that in the case of HBV this has not been widely practised in the United Kingdom [Jibani *et al* 1994].

11.4 In May 1995, the Department of Health asked the Public Health Laboratory Service (PHLS) to prepare advice, in the form of draft guidelines, on the precautions that should be taken in renal units to prevent the transmission of BBV in general. A working party was set up which included representatives of the Royal College of Physicians and the Royal College of Pathologists. Their document was submitted to the Department in late 1996 and is currently under review. When the Department makes its comprehensive report, its recommendations will become the norm.

■ ***In the interim we recommend the following practices***

Routine precautions against BBV

11.5 Staff should strictly observe barrier precautions against exposure to blood, and good hygiene and infection control practice, in the treatment of all dialysis patients. The staffing levels and the environment of the dialysis units should be designed to allow for safe working practices. The safety aspect of the environment should be reviewed at regular intervals and whenever a virus transmission has been recognised in the unit. Precautions in the use of disposables and machines and their cleaning or sterilisation should be of the highest standards and should be reviewed regularly. Units should have a policy for the reporting and the management of incidents involving exposure to blood.

Immunisation and prophylaxis

11.6 Units in the UK practising immunisation have reported low (ca 40%) successful (>10 mIu/ml) primary immunisation rates in patients already on dialysis, with an increase to only 60% at best after 'booster' doses. This is in line with the published data from elsewhere [eg Köhler *et al* 1984]. Whilst other strategies such as the use of recombinant vaccines and intradermal injection can improve results [Ono and Kashiwagi 1991], this requires greater expense and investment of time, and a good proportion of patients (ca 30%) will still remain unprotected. In view of the very low prevalence of hepatitis B surface antigen (HBsAg) in dialysed patients in the United Kingdom, the cost effectiveness of this approach needs to be established. We therefore recommend that, whenever possible, patients should be immunised while in the low clearance clinic before they reach end stage renal failure (ESRF). At plasma creatinine concentrations as low as 200–400 μmol/l, response is nearly as poor as in patients already on dialysis [Köhler *et al* 1984], but starting early allows more time for immunisation to become effective before its benefits are needed.

Recommended standard

Patients awaiting start of ESRF treatment should be immunised against HBV as soon as possible while their plasma creatinine remains relatively low. **(B)**

All long term dialysis patients should be immunised against HBV. Those who develop an adequate antibody response should be given a booster dose of vaccine every 5 years. As there is evidence that non-responders and poor responders derive some benefit from vaccination, they should be given a booster after 1 year and every 5 years thereafter. **(B)**

Hepatitis B immunoglobulin and vaccine should be given, if appropriate, to susceptible patients who have been exposed to the virus. **(B)**

Testing patients for BBV

11.7 A point of contention is the *frequency with which stable uninfected patients on dialysis should be tested*, which has major cost implications. Most UK renal units do not test for HBs antigen more frequently than every 3 or (more usually) 6 months; this is felt by us to be reasonable as routine practice in view of the low prevalence of HBsAg carriage in British dialysis patients. With regard to HIV, the prevalence is very different in different parts of the country (eg rural versus some metropolitan) and with age (extremely rare in the elderly), so routine frequency of testing may vary according to location. For hepatitis C (HCV), again given the low prevalence in UK units, 6-monthly testing seems adequate except after an outbreak has occurred. All patients should have at least an annual test for all BBV.

Recommendation

Testing should be carried out every 3 months for HBsAg, every 6 months for HCV antibody and annually for HIV antibody. An annual test for HBsAg is sufficient for patients who have demonstrated immunity. **(B)**

The patient's informed consent to testing should be obtained where possible. Those who withhold consent should be managed as though they were BBV infected. However, infected patients should not be denied dialysis. **(B)**

Segregation of patients carrying BBV

11.8 Although universal precautions are appropriate against all BBV, hepatitis B is much more infective than either HIV or hepatitis C. Patients carrying hepatitis B should have dedicated dialysis monitors and where possible occupy a segregated area within the dialysis unit; nursing traffic between these two areas should be reduced to a minimum.

11.9 In contrast, the management of patients who are carriers of hepatitis C is controversial [Sampietro *et al* 1996], particularly those proved to carry the antigen, but also those with antibodies that may be non-neutralising. Whilst transmission of HCV from patient to patient within dialysis units ('sideways transmission') undoubtedly can take place [Stuyver *et al* 1996], the predominant route is by infected blood; whether the segregation of carrier patients is useful in preventing cross-infection remains in doubt and may even have deleterious consequences if patients segregated together carry different strains of the virus [Jadoul 1995]. The American Centers for Disease Control [Moyer and Alter 1994], the German Nephrology Group on hepatitis, and the authors of a recent detailed review [Pereira and Levey 1997] all recommend universal precautions only, proven in at least two epidemics in dialysis units to be effective when applied alone [Niu *et al* 1992; Okuda *et al* 1994].

11.10 The space implications for dialysis units of patient segregation for BBV, when taken with the need to cope with methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant organisms (see below) are considerable, optimum use of staff is disrupted, and further costs are incurred. There is some evidence that use of *dialysis monitors* ('machines') for more than one patient can result in transmission of HCV to successive patients ('vertical transmission') [Simon *et al* 1994], though the contrary view has been sustained [Gilli *et al* 1995]. For the moment we recommend that monitors be reserved for the use of BBV carrier patients only; this forms part of the German Nephrology Group recommendations. There is evidence that this is as effective as separate rooms in reducing hepatitis C carriage rates in high prevalence units [Pinto dos Santos *et al* 1996].

11.11 Evidence concerning re-use of dialysers is not yet clear; in the paper just cited re-use made no difference to cross-infection rates, but it seems prudent for the moment *not* to practise re-use, which exposes staff to the risk of infection and requires separate re-use facilities (see 5.4–5.6). It is not yet clear, given the different serotypes of hepatitis C that may be found [Jadoul 1996], whether *each* hepatitis C patient should have a designated monitor. Clearly this cannot be practised in countries or units with a prevalence of hepatitis carriage rates of 10–40% in their dialysis populations.

Recommendation

Whenever possible, staff should care for only BBV infected *or* uninfected patients during one shift. If this is not practicable, the more experienced staff should be assigned the task of caring for a mixed group of patients. Designated staff should nurse affected patients when there has been an outbreak of BBV infection in a unit. In the case of hepatitis B, staff who have demonstrated immunity should care for the patients whenever possible. (**C**)

Carriers of hepatitis B should be dialysed separately on dedicated machines. (**C**)

Carriers of hepatitis C should be dialysed where possible in separate or single shifts, but need not be isolated in separate rooms. (**C**)

Dialysis monitors ('machines') used for hepatitis C carrier patients should not be used for non-infected patients. Disposables and dialysers from these patients should not be re-used until further evidence accumulates. (**C**)

Carriers of HIV should be managed as for hepatitis C. (**C**)

Patients who have dialysed in another unit

11.12 When patients have dialysis in a unit in a country with high carriage rates for hepatitis B and/or C the risk is considerably greater than in a unit in the UK that implements the protocols discussed above; this must be taken into account in recommendations for their management on return. Those who have *dialysed abroad*, during the incubation period of the various BBV, should be treated as potentially infected. In contrast, testing for BBV at monthly intervals for 4 months without segregation should be adequate for those who have *dialysed in another British unit*, provided that, during their time there, they have not been accidentally exposed to a possibility of infection, eg use of a machine designated for BBV positive patients.

Staff

11.13 Clearly those working in a dialysis environment must be protected as far as possible against acquisition of BBV from patients or patient related materials. For hepatitis B this can be achieved most efficiently by testing for immunity to the virus and then immunising those who do not demonstrate it. At the moment however there is no effective immunisation against other BBV, which emphasises again the importance of universal precautions. Staff demonstrated to be carriers of BBV should not work in dialysis units and will need counselling and career advice. Family and other carers actively involved in dialysis should be considered in the same way as unit staff.

Recommended standard

Staff working in dialysis units in contact with patients, machines or materials used in dialysis should be tested for immunity against HBV. There is no need for regular HBsAg testing for those who demonstrate immunity to HBV. (**A**)

Those who do not demonstrate immunity should be immunised against HBV. Those developing an adequate antibody response should be given a booster dose of vaccine 5 years after the primary course. Non-responders and poor responders should be given a further course or dose respectively. Staff who have not demonstrated immunity should be tested annually. (**A**)

Staff who are HBeAg* positive should not work in clinical contact with patients.

Staff who are found to be HCV or HIV positive should be referred for occupational health advice about employment in a dialysis unit.

** The recent recognition that some HBeAg negative, HBsAg positive carriers infected with mutant strains of hepatitis B can transmit the infection to patients during invasive procedures [Incident investigation teams and others 1997] may well call for more stringent precautions. Pending the publication of the Department of Health's report, we recommend that HBeAg negative, HBsAg positive carriers should not perform invasive procedures in the renal unit.*

Patients treated by CAPD

11.14 Universal precautions should be sufficient to avoid cross-infection from and to patients on continuous ambulatory peritoneal dialysis (CAPD) while in hospital (eg for training or owing to peritonitis); we do not recommend that these patients be isolated in separate rooms.

BBV and patients in CRF not yet on dialysis

11.15 Precautions should be observed for patients in *CRF not yet on dialysis* in exactly the same way as for those on dialysis. Testing for BBV should be routine in those entering CRF (low clearance) clinics, but it is not possible yet to recommend whether or how often this should be repeated. As noted above, immunisation for HBV is best carried out in the CRF clinic.

BBV and patients in ARF

11.16 Patients presenting in *ARF requiring dialysis* should be managed according to the universal principles outlined in the recommendations above, with the exception of advice relating to long term follow-up. Until results of BBV tests are available, such patients should be assumed to be carriers of BBV. In any case, an open regular dialysis unit is not a suitable site in which to perform dialysis on these sick patients.

■ ***Transplanted patients are discussed below.***

Methicillin resistant *Staph. aureus*

11.17 Increasing numbers of patients are or become colonised with MRSA [Goldman *et al* 1996]. Although not in general more pathogenic than other staphylococci, some more virulent strains have been noted recently, and their spread through renal units has implications for antibiotic use, for example the need to use vancomycin as first-line treatment for prophylaxis against staphylococcal infections [Strausbaugh and Bennett 1996]. It is clearly of the first importance to prevent spread of the organism by members of staff. This should be part of a hospital-wide cross-infection policy.

Patients already colonised

11.18 Good nursing practice can do much to avoid spread of these organisms in the unit. Patients colonised with MRSA must be barrier nursed in isolation from other patients both in the ward and in the dialysis or transplant unit. This is to prevent the spread of organisms on the hands of *members of staff*, which is believed to be the principal route of spread. When seen in outpatients, colonised patients should be separated as much as is possible from other patients, eg given appointments at the end of the clinic or seen in a different room. Where possible, dedicated staff should be allocated to such patients with as little contact with non-contaminated patients as is practicable. Doctors and nurses must wash their hands

before and after contact with such patients, and wear gloves, above all if handling any skin lesions or wounds.

11.19 For this purpose there must be sufficient isolation rooms in the renal ward to accommodate such patients, in addition to those with BBV; this has implications for both planning and costs. In some instances such facilities may be more readily available, and cross-infection policies more strictly adhered to in an infectious disease ward, bearing in mind the clinical condition and needs of the patient.

11.20 Patients who do not have open wounds or exposed prosthetic materials, eg indwelling subclavian lines for haemodialysis or peritoneal dialysis catheters, can be decolonised. Criteria for decolonisation vary, but many units employ a criterion of three successive negative swabs, when the patient is not being treated with antimicrobials, from a site at which carriage has been previously demonstrated. Whether the effort and cost of identifying and decolonising patients who are MRSA carriers is justified remains controversial [Bowler 1997; Cookson 1997; Pittet and Waldvogel 1997; Teare and Barrett 1997]. It is our view that until the safety of not taking this precaution has been demonstrated it should be continued. Identification of staff carriers of MRSA, change in duties and decolonisation are even more controversial practices which are not currently recommended.

Patients at high risk of colonisation

11.21 Patients at risk of already being colonised, eg those admitted from hospitals or wards with a known high prevalence of MRSA, should be assumed to be contaminated until a set of nasal and skin swabs has been shown to be negative. These should be taken from sites of staphylococcal colonisation (nose, axillae, perineum, wounds and throat). The patients should be allowed on to the main ward or unit only when the swabs have been shown to be negative.

Recommendation

Facilities and policies for the containment of MRSA in renal units must be available and should be drawn up with the local infection control team.

Patients colonised with MRSA must be isolated from other patients both in the ward and in the dialysis unit, and only re-admitted to these facilities when they have been demonstrated to be clear of contamination. (**C**)

At consultations in outpatients or in hospital, doctors, nurses, phlebotomists and other staff must wash their hands with alcohol or alcohol-containing scrub before and after contact, and wear gloves. (**B**)

Clostridium difficile

11.22 This organism is the cause of either diarrhoea or *pseudomembranous colitis*, a common complication caused by overgrowth of the responsible organism in elderly, frail and frequently hospitalised patients. It is endemic and epidemic in many renal units; many symptomless patients harbour the organism but only become clinically ill when debilitated by other events, particularly treatment with antibiotics, above all during long term treatment with broad spectrum cephalosporins. There is evidence of cross-infection while in the ward.

11.23 The incidence can be reduced by limitation of prolonged courses of broad spectrum antibiotics, especially cephalosporins, and by prophylactic administration of *saccharomyces* [McFarland *et al* 1995]; brewer's yeast has been used for the same purpose but its value is unproven.

11.24 Patients developing pseudomembranous colitis should be barrier nursed in isolation, and their faeces disposed of with appropriate precautions. Nurses and doctors caring for patients with *C. difficile* must practise strict cross-infection precautions. After discharge the room should be cleaned with dilute hypochlorite before another patient is admitted.

Recommendation

Renal units must have facilities and policies for the containment and treatment of *C. difficile* enterocolitis. **(C)**

Vancomycin resistant organisms

11.25 A recent development has been the appearance of organisms (*Enterococcus, Staph. aureus* and *Staph. epidermidis*) resistant to vancomycin, largely as a result of veterinary use of related antibiotics, which was banned in late 1996 by the European Union. These organisms, although encountered in all areas of medicine, are found especially in patients on CAPD with peritonitis, which suggests that the use of vancomycin as a primary 'blind' antibiotic should be reassessed [Golper and Tranaeus 1996]. However, the organisms may be encountered in a variety of other clinical circumstances in the renal unit, including where vancomycin is used to treat line infections in haemodialysed patients, and again the use of this antibiotic should be minimised [Strausbaugh and Bennett 1996].

Microbiology in transplantation

The NHS Executive has published *Guidance on the microbiological safety of human tissues and organs used in transplantation* [Department of Health 1996b]. We quote from this document in the next paragraphs.

BBV in potential donors

11.26 The NHS Executive working party report advocates that a donor history relevant to possible blood- or tissue-borne infections should be taken, including a family history. This will be possible for living donors, but difficult for cadaver donors. Enquiries should be made about a family history of Creutzfeldt-Jakob disease (CJD), previous treatment with natural growth hormone, or undiagnosed degenerative neurological disorders. 'These individuals should not be used as donors.' Where possible a history of sexual practices should also be obtained, and if it is clear that they have been exposed to situations known to have a high risk of HIV transmission (listed in the report) 'their kidneys should not be used for transplantation'. Those with possible rabies, tuberculosis or a past history of malaria are likewise to be excluded.

11.27 Serological testing of potential donors 'should be carried out for the following pathogens in accordance with standard operating procedures where available':

- HIV-1 and HIV-2 antibody

- HCV antibody (using a test method evaluated by the PHLS or the Scottish National Blood Transfusion Service)
- HBsAg

Donors with serum positive for any of the above 'must not be used for transplantation'. The consequences for possible partners and families of those found to be positive must not be forgotten, and the hospital concerned and the general practitioner of the donor will need to be notified of the result.

- Cytomegalovirus (CMV) antibody

'Wherever possible anti-CMV positive donors should be used only for anti-CMV positive recipients.'

- Syphilis antibody
- Toxoplasma

'should be tested for routinely'.

These last two tests are *not* practised in British transplant units, and their utility seems doubtful in view of the low carriage rates in the UK. We do not have evidence of transmission of either toxoplasmosis or syphilis via a transplanted organ in the UK, although examples of the latter have been reported from the USA.

Bacterial and other infections in potential donors

11.28 Whether a donor with infection may or should not be used is a decision that can only be taken by those retrieving the organs after discussion with a microbiologist experienced in transplantation. The NHS Executive guidance document lists a number of infections that need to be discussed with particular care.

Microbiology post-transplantation

11.29 The care of patients taking immunosuppressive drugs following transplantation requires particularly close cooperation with a microbiologist and/or infectious disease specialist experienced in this field. Staff must be aware that both usual and unusual nosocomial opportunistic organisms may be encountered, as well as organisms already present on or within the recipient. It is particularly important that treatable pathogens such as *Mycobacterium tuberculosis* or exotica such as *Strongyloides* should not be forgotten. The possibility of combined bacterial and viral, or bacterial and fungal, infections must be borne in mind constantly. No recommendations can be made at the moment, but particular areas in which further data are needed include the following.

Prophylactic antibiotics

11.30 The use of *prophylactic antibiotics* during and immediately after transplantation. Published data describing benefit from this approach refer almost entirely to patients receiving immunosuppressive regimens much greater than those usual today, and it has not been established what current practice should be, although encouraging reports have appeared, including the prospective controlled trial of Fox *et al* [1990].

11.31 For prophylaxis against *Pneumocystis carinii*, many units give co-trimoxazole orally, or pentamidine by inhalation if the patient is allergic to co-trimoxazole, for varying periods following transplantation. The benefits, costs and disadvantages of these regimens have never been assessed fully in patients using current immunosuppressive regimes, though one controlled trial [Elinder *et al* 1992] in 375 renal and renal-pancreas transplants showed clear benefit.

Recommendation

Renal transplant recipients should receive prophylaxis for 6 months post-transplant using co-trimoxazole 480 mg daily **(A)**

Tuberculosis

11.32 The management of patients at special risk for *M. tuberculosis* infections remains uncertain. These include patients of Asian, African and Afro-Caribbean origin, patients from areas of the world with a high prevalence of tuberculosis, and patients with a history of treated tuberculosis. Many units use prophylaxis isoniazid alone 100 mg daily which has been accompanied by disappearance of previously common post-transplant tuberculosis in these groups. However, the strength of the data is insufficient to permit a recommended standard at the moment, and there are increasingly numerous reports of isoniazid resistant organisms worldwide.

Cytomegalovirus

11.33 The management of CMV infection in transplantation is contentious [Syndman *et al* 1993; Newstead 1995; Patel *et al* 1996], in part because different definitions of clinical 'disease' have been used, varying from simple seroconversion to serious clinical syndromes. A number of related problems such as *de novo* infection with CMV and re-activation of virus already present have been reported together as though they were the same. Finally, data from patients receiving transplants of organs other than the kidney, or with HIV infection, having different degrees of immunosuppression have been generalised to apply to kidney transplantation. However, it is clearly established that the use of protein immunosuppression (ALG, ATG, OKT3 etc) is associated with a particularly high incidence of more severe clinical disease, with a considerable mortality if the CMV is untreated [Syndman *et al* 1987; Newstead 1995].

11.34 It is important to know whether or not an individual has acquired some immunity against CMV. In the British dialysis population, approximately 50% of recipients are CMV antibody positive [Newstead 1995], and population studies abroad have shown this to be strongly related to age, rising from 20% in the young to 80% of the elderly population.

Recommended standard

All patients being considered for transplantation should be tested for the presence of plasma antibodies directed against CMV. **(B)**

Prophylaxis in CMV antibody positive recipients

11.35 Re-activation of CMV in an anti-CMV antibody positive patient who is still carrying the virus is common, so latent infection becomes clinically evident. This will be more common the more intense the immunosuppressive regime, but in general these patients are at low risk of developing CMV disease.

■ ***No prophylaxis is recommended in CMV positive recipients, but severe clinical disease will of course require treatment.***

Prophylaxis in CMV antibody negative recipients

11.36 The more difficult problem is *transplantation into CMV antibody negative recipients*, who are particularly likely to acquire *de novo* CMV infection under immunosuppression, even if a CMV negative kidney is used as recommended in Chapter 7. The *placement of CMV positive kidneys into CMV negative recipients* is particularly worrying, and presents unresolved problems. This should be avoided if possible, but will be indicated when there is difficulty in obtaining a donor organ, in obtaining a particularly good tissue match or in living donor transplantation. In the United Kingdom, approximately 60% of CMV negative recipients receive CMV positive kidneys, of whom 50% will go on to develop clinical disease from 6–8 weeks after transplantation, requiring hospital admission for an average of 8 days [Newstead 1995]. Although the disease is most often mild, it can be severe or even life threatening.

■ ***Whether CMV antibody negative patients should receive prophylaxis, and if so by what method, has not been determined.***

11.37 Prophylaxis with *aciclovir* has given encouraging results in a few studies [eg Balfour *et al* 1989], but most studies have found little or no effect (summarised by Goral *et al* [1996]) and its use cannot be recommended.

11.38 *Oral ganciclovir* is poorly and irregularly absorbed, but there is evidence from a prospective controlled trial in liver transplant recipients that 3 g/24 h is effective in reducing the incidence of clinical infection [Gane *et al* 1996]. *Intravenous ganciclovir* for only 1–3 weeks has been effective in some studies [Leray *et al* 1995] but in other studies it proved ineffective [Rondeau *et al* 1993]. Prolonged intravenous administration (10–12 weeks or more) presents practical difficulties in outpatients, carries a significantly higher chance of serious side effects, and is expensive.

11.39 Passive immunoprophylaxis has been the subject of a controlled trial in the United Kingdom, as yet unpublished; previous studies have shown encouraging results using hyperimmune globulin [Syndman *et al* 1987], especially in reducing mortality (but not necessarily incidence) of clinical CMV infection in patients who had received immunosuppressive antibodies. (At the time of writing in 1997, this product is under review for commercial release.)

11.40 *Active immunoprophylaxis* of CMV negative patients using the Towne strain of virus has been used but is not particularly effective.

11.41 *At the moment no recommended standards are possible in this area. However, it is common practice that CMV negative patients receiving a CMV positive kidney are given routine prophylaxis if they have received treatment with immunosuppressive antibodies (ALG, ATG, OKT3 etc).* If no prophylaxis is given to other patients, they must be observed closely from the third week following engraftment every 2–3 weeks for 3 months, or tested if there is any clinical suspicion of disease. Tests for CMV antigen (direct antigen test or preferably PCR), together with measurement of IgM anti-CMV antibodies should be performed. If patients become either CMV antigen or antibody positive, they should be treated promptly even if they have no clinically evident disease.

11.42 *Prophylaxis, if given, should be with oral ganciclovir in a dose adjusted for renal function, from weeks 2–10 following transplantation, or by intravenous ganciclovir for a similar period.* There is a case to suggest that those who have received immunosuppressive antibodies should receive in addition intravenous hyperimmune globulin every two weeks at 100 mg/kg ideal body weight.

11.43 In treating patients with CMV, the immunosuppressive potential of this infectious agent must not be overlooked, and it is common to find that there is superinfection with other agents. The degree by which immunosuppression is reduced and the intensity of treatment of the CMV will vary with the clinical severity of the disease.

Hepatitis C positive patients

11.44 *Potential recipients who are shown to be hepatitis C positive* on screening (see 11.5) present major problems, since there is good evidence that their liver disease may become active or worsen under immunosuppressive treatment, to the point of requiring liver replacement for liver failure. Liver biopsy findings can help discriminate this poor prognosis group (chronic active hepatitis) from those with a lesser risk (normal liver or milder forms of liver pathology), but the efficacy of α-interferon is not yet known for this situation. No recommendations can be made at the moment.

12 Quality of life

12.1 We recognise the crucial importance of quality of life (QOL) assessment [Testa and Simonson 1996] in chronic disorders such as those affecting many patients with renal disease [Evans *et al* 1985; Gudex 1995; McGee and Bradley 1995]. Assessment usually depends upon one of two approaches: the level of function, such as mobility (eg the Karnovsky index [Gutman *et al* 1981]), ability to enter employment or study; and subjective assessments of mood, feeling, attitude and sense of well-being, or lack of it, using a great variety of different methods [Barratt *et al* 1990].

12.2 However, despite a good deal of work in this area to develop suitable instruments for standard use [Gill and Feinstein 1994], such as the Short Form 36, and others especially for use in renal patients (eg Hays *et al* [1994] which describes the kidney disease QOL (KDQOL)^{TM} instrument), at the time of preparing this report there are no agreed methods of assessment upon which audit of this aspect of renal care can be based.

12.3 The Renal Association Executive receives regular reports from an informal national working group on QOL issues in renal medicine, and in the future we hope to be able to make recommendations in this important area.

Appendix 1

Renal services described for non-physicians

This annex gives information on the issues discussed above in this document, provides background information on renal failure, and discusses the services available for its treatment.

Renal disease

A1.1 Diseases of the kidney are not as common as cardiovascular conditions or cancers but are much more common than some well known disorders such as multiple sclerosis or muscular dystrophy. Renal conditions account for about 7,000 deaths per annum according to the Registrar General's figures, but these are probably an underestimate since about one-third of deaths of patients with renal failure are not recorded as such in mortality statistics. These figures exclude deaths from cancers of the kidney and associated organs of the urinary tract such as bladder and prostate.

A1.2 Over 100 different diseases affect the kidneys. These diseases may present early with features such as pain, the presence of blood or protein in the urine, or peripheral oedema (swelling in the legs), but much renal disease is self-limiting; it occurs and heals with few or no symptoms or sequelae. On the other hand, some kidney diseases start insidiously and progress but are undetected until renal failure develops.

Acute renal failure

A1.3 Renal failure may be acute and reversible. It occurs in previously normal kidneys when their blood supply is compromised by a fall in blood pressure caused by crush injuries, major surgery, failure of the heart's pumping action, loss of blood, salt or water, or when they are damaged by poisons or overwhelming infection. Renal support is then needed for a few days or weeks before renal function returns. However, about half such patients die during the illness because of other conditions.

Chronic renal failure

A1.4 More common is *chronic irreversible renal failure*, in which the kidneys are slowly destroyed over months or years. To begin with there is little to see or find, and this means that many patients present for medical help very late in their disease, or even in the terminal stages. Tiredness, anaemia, a feeling of being 'run down' are often the only symptoms. However, if high blood pressure develops, as often happens when the kidneys fail, or is the prime cause of the kidney disease, it may cause headache, breathlessness and perhaps angina. Ankle swelling may occur if there is a considerable loss of protein in the urine.

A1.5 Progressive loss of kidney function is often described as chronic renal insufficiency when in its early stages, chronic renal failure when it becomes obvious, and end stage renal failure when it reaches its terminal stage. At this point, if nothing is done, the patient will die. Two complementary forms of treatment — dialysis and

renal transplantation — are available and both are needed if end stage renal disease is to be treated.

A1.6 The incidence of end stage renal failure rises steeply with advancing age. Consequently an increasing proportion of patients treated for end stage renal failure in this country are elderly and the proportion is even higher in some other developed countries. Evidence from the United States suggests that the relative risk of end stage renal failure in the black population (predominantly of African origin) is two to four times higher than for whites [US Renal Data System 1993]. Data collected during the review of renal specialist services in London suggest that there is in the Thames regions a similar greater risk of renal failure in certain ethnic populations (Asian and Afro-Caribbean) than in whites [Roderick *et al* 1994]; this is supported by national mortality statistics [Raleigh *et al* 1996]. People from the Indian subcontinent have a higher prevalence of non-insulin dependent diabetes, and those with diabetes are more likely than whites to develop renal failure. This partly explains the higher acceptance rate of Asians on to renal replacement programmes.

Causes of renal failure

A1.7 Most renal diseases that cause renal failure fall into a few categories.

i *Autoimmune disease*. 'Glomerulonephritis' or 'nephritis' describes a group of diseases in which the glomeruli (the filters that start the process of urine formation) are damaged by the body's immunological response to tissue changes or infections elsewhere. Together, all forms of nephritis account for about 30% of renal failure in Britain. The most severe forms are therefore treated with medications that suppress the immune response, but treatment makes only a small impact on the progress of this group of patients to end stage renal failure

ii *Systemic disease*. Although many generalised diseases such as systemic lupus, vasculitis, amyloidosis and myelomatosis can cause kidney failure, by far the most important cause is diabetes mellitus (about 20% of all renal disease in many countries). Progressive kidney damage may begin after some years of diabetes, particularly if the blood sugar and high blood pressure have been poorly controlled. Careful lifelong supervision of diabetes has a major impact in preventing kidney damage.

iii *High blood pressure*. Severe ('accelerated') hypertension damages the kidneys, but the damage can be halted — and to some extent reversed — by early detection and early treatment of high blood pressure. This is a common cause of renal failure in patients of African origin.

iv *Obstruction*. Anything that obstructs the free flow of urine can cause backpressure on the kidneys. Much the commonest cause is enlargement of the prostate in elderly men; although only a small proportion of them develop kidney failure, prostatism is so common that it becomes a major cause of renal failure over the age of 70 [Feest *et al* 1990, 1993].

v *Infection of the urine*. Cystitis is a very common condition, affecting about half of all women at some time in their lives, but it rarely has serious consequences. However, infection of the urine in young children or patients with obstruction, kidney stones or other abnormalities of the urinary tract may result in scarring of the kidney and eventual kidney failure.

vi *Genetic disease*. One common disease, polycystic kidneys, and many rare inherited diseases affecting the kidneys account for about 8% of all kidney failure in Britain. Although present at birth, polycystic kidney disease often causes no symptoms until middle age or later. Understanding of its genetic basis is rapidly advancing and may lead to the development of effective treatment.

vii *Disease of renal blood vessels*. This is being more and more frequently recognised as a cause of renal failure, both acute and chronic. It is especially common in patients aged more than 65 years.

Prevention

A1.8 Although many diseases causing chronic renal failure cannot be prevented or arrested at present, better control of diabetes and high blood pressure and relief of obstruction have much to offer, provided they are employed early in the course of the disease before much renal damage has occurred. Screening for renal disease has not been widely practised, because the relatively low incidence of cases renders population screening inefficient and costly. Urine tests for protein or blood, or blood tests for the level of some substances normally excreted by the kidney such as creatinine and urea, are potentially useful methods for screening, if populations at risk for renal failure can be identified, eg diabetics and the elderly.

Comorbidity

A1.9 Renal failure is often accompanied by other disease processes. Some are due to the primary disease, eg diabetes may cause blindness and diseases of the nerves and blood vessels. Others, such as anaemia, bone disease and heart failure, are consequences of the renal failure. Coincidental diseases such as chronic bronchitis and arthritis are particularly common in older patients with renal failure. All these conditions, collectively called comorbidity, can influence the choice of treatment for renal failure and may reduce its benefits. Expert assessment of the patient before end stage renal failure can reduce comorbidity and increase the benefit and cost effectiveness of treatment. Thus early detection and referral of patients at risk of renal failure is important. Studies in France and in the United States showed that the mortality rate among patients aged over 55 years at the start of regular dialysis increased dramatically if dialysis was started late in the illness [Jungers *et al* 1993; Byrne *et al* 1994].

Renal replacement therapy

A1.10 The term renal replacement therapy is used to describe treatments for end stage renal failure in which, in the absence of kidney function, the removal of waste products from the body is achieved by dialysis and other kidney functions are supplemented by drugs. The term also covers the complete replacement of all kidney functions by transplantation.

Therapeutic dialysis ('renal dialysis')

A1.11 Dialysis involves the removal of waste products from the blood by allowing these products to diffuse across a thin membrane into dialysis fluid which is then discarded along with the toxic waste products. The fluid is chemically composed to draw or 'attract' excess salts and water from the blood to cross the membrane, without the blood itself being in contact with the fluid.

Haemodialysis

A1.12 The method first used to achieve dialysis was the artificial kidney, or haemodialysis. This involves the attachment of the patient's circulation to a machine through which fluid is passed, and exchange can take place. A disadvantage of this

method is that some form of permanent access to the circulation must be produced to be used at every treatment. Each session lasts 4–5 hours and is needed three times a week.

Peritoneal dialysis

A1.13 The alternative is peritoneal dialysis, often carried out in the form of continuous ambulatory peritoneal dialysis (CAPD). In this technique, fluid is introduced into the peritoneal cavity (which lies around the bowel) for approximately 6 hours before withdrawal. The washing fluid must be sterile in order to avoid peritonitis (infection and inflammation of the peritoneum), which is the main complication of the treatment. A silastic tube must be implanted into the peritoneum and this may give problems such as kinking and malposition. Each fluid exchange lasts 30–40 minutes and is repeated three or four times daily.

Neither form of dialysis corrects the loss of the hormones secreted by the normal kidney so replacement with synthetic erythropoietin and vitamin D is often necessary.

Renal transplantation

A1.14 Renal transplantation replaces all the kidney's functions, so erythropoietin and vitamin D supplementation are unnecessary. A single kidney is placed, usually in the pelvis close to the bladder, to which the ureter is connected. The kidney is attached to a nearby artery and vein. The immediate problem is the body's acute rejection of the foreign graft, which has largely been overcome during the first months using drugs such as steroids and cyclosporin. These drugs, and others that can be used for that purpose, have many undesirable side effects, including the acceleration of vascular disease, so myocardial infarcts and strokes are commoner in transplant patients than in age matched controls. During subsequent years there is a steady loss of transplanted kidneys owing to a process of chronic rejection; treatment of this is quite unsatisfactory at the moment, so many patients require a second or even a third graft over several decades, with further periods of dialysis in between.

A1.15 The main problem with expanding transplantation is the shortage of suitable kidneys to transplant. Although the situation can be improved it is now clear that, whatever social and medical structures are present and whatever legislation is adopted, there will inevitably be a shortage of kidneys from humans. This remains the case even if kidneys from the newly dead (cadaver kidneys) are retrieved with maximum efficiency, and living donors (usually but not always from close blood relatives of the recipient) are used wherever appropriate. Hope for the future rests with solving the problems of xenotransplantation (that is using animal kidneys), probably from pigs, although baboons have also been suggested and are closer to humans. Many problems remain unsolved and it is thought highly unlikely that xenotransplantation will become a reliable treatment for end stage renal failure within the next 10 years.

Nature of renal services

A1.16 The work of a nephrologist includes the early detection and diagnosis of renal disease and the long term management of its complications such as high blood pressure, anaemia and bone disease. The nephrologist may share the management with the general practitioner or local hospital physician, and relies on them to refer

patients early for initial diagnosis and specific treatment. At any one time perhaps only 5% of patients under care are inpatients in wards, the remainder being treated in their homes, another 20% attending the renal unit regularly for haemodialysis. *However, inpatient nephrology and the care of patients receiving centre-based dialysis is specialised, complex and requires experienced medical advice to be available on a 24 hour basis*. This implies sufficient staff to provide expert cover; cross-covering by inexperienced staff is inappropriate and to be condemned. The other 95% of renal work is sustained on an outpatient basis; this includes renal replacement therapy by dialysis and the care of transplant patients.

A1.17 There are five major components to renal medicine:

i *Renal replacement therapy*. The most significant element of work is in relation to the preparation of patients in end stage renal failure for renal replacement therapy and their medical supervision for the remainder of their lives. The patient population will present increasing challenges for renal staffing as more elderly and diabetic patients are accepted for treatment.

ii *Emergency work*. The emergency work associated with the specialty consists of:

- Treatment of acute renal failure, often involving multiple organ failure and acute-on-chronic renal failure. Close cooperation with other medical specialties, including intensive care, is therefore a vital component of this aspect of the service.

- Management of medical emergencies arising from an end stage renal failure programme. This workload is bound to expand as the number and age of patients starting renal replacement therapy increase, and this may interrupt the regular care of patients already on renal replacement therapy, so increased resources may be required

iii *Routine nephrology*. A substantial workload is associated with the immunological and metabolic nature of renal disease which requires investigative procedures in an inpatient setting. It is estimated that 10 inpatient beds per million of the population are required for this work.

iv *Investigation and management of fluid and electrolyte disorders*. This is a variable proportion of the nephrologist's work, depending on the other expertise available in the hospital

v *Outpatient work*. The outpatient work in renal medicine consists of the majority of general nephrology together with clinics attended by dialysis and renal transplant patients.

(Further details of renal services for renal failure, written for non-physicians, can be found in: Cameron JS. *Kidney failure — the facts*. London: Oxford University Press, 1996.)

Appendix 2

Special arrangements for children

This appendix, which outlines and comments on additional requirements for the treatment and audit of children with renal disease, has been submitted by the British Association for Paediatric Nephrology whose document *The provision of services in the UK for children and adolescents with renal disease* [1995] describes in detail the service requirements for a paediatric nephrology unit. Three important principles can be abstracted from that document:

- Children with renal disease are children first and foremost. Any unit offering care for children and young people with renal disease would be expected fully to implement the Department of Health [1991] guidelines.
- A high quality paediatric renal service must be family orientated and delivered by a multidisciplinary team that includes specialist nursing, child psychiatry and psychology, dietetics, social work, teaching and play therapy, in addition to medical and surgical staff.
- All children with renal disease should be investigated and treated by paediatricians, paediatric nephrologists, paediatric urologists, paediatric surgeons and paediatric anaesthetists.

The numbers against the following items refer to paragraphs in the main document:

1.15 Risk factors vary with age even during childhood, with mortality at its highest in the very young. For example, patient survival at 2 years after renal transplantation is 82% in those less than 2 years of age, 93% in those aged 2–5 years and 97% in 6–14 year olds [European Renal Association 1996]. Comorbidity may be an important factor in children with multiple congenital abnormalities.

3.1 Many families of children with renal failure find CAPD less disruptive to family life than hospital based haemodialysis. There is no evidence in children that morbidity is increased above that of haemodialysis.

4.8 The number of children entering ESRF programmes has shown a steady rise, from 6.6 per million of the child population (aged <15 years) in 1984, to 7.4 pmcp in 1986 and 9.7 pmcp in 1992. This currently represents an annual rate of presentation of 2–5 per million population. The increase in acceptance rates is principally due to the treatment of infants. However, the total number of new patients is small (446 in the UK in 1992), and therefore to maintain expertise the care of these children must be in specialised paediatric nephrology centres [British Association for Paediatric Nephrology 1995].

5.16 Bicarbonate dialysis should be universal for children.

5.20 Children should be treated in an environment sympathetic to their needs, including the provision of in-house teaching and play therapy where appropriate. Dialysis treatment should be as painless and free from symptoms as possible and include the monitoring of symptoms such as vomiting and hypotension and cramps.

5.28 The normalised *Kt/V* and nitrogen appearance rate (protein catabolic rate, PCR) have been validated as tools to measure haemodialysis treatment in children. The optimum values have yet to be defined but, because of the greater metabolic needs of the child compared with adult patients, should probably lie between a *Kt/V* of 1.2 and 1.5.

5.28 & 5.35 Both adequacy of dialysis and nutritional status can also be assessed in children by their rate of increase in height and head circumference. Some children may need enteral feeding to achieve adequate nutrition.

5.37 Blood pressure increases throughout childhood, and should be maintained within 2 standard deviations (SD) of the mean for normal children of the same height.

5.38 The normal range for plasma phosphate decreases throughout childhood, and should be kept within 2 SD of the mean for age.

5.39 There is no evidence that an intact parathormone above the normal range is beneficial in childhood, and it should be maintained below twice the upper limit of the normal range.

5.42 Vascular access should take into account the age of the child, and where central lines are used the rate of infection should be less than 1 every 12 patient-months.

5.53 Rates of hospitalisation do not reflect morbidity in children. Infants with structural abnormalities require frequent admissions for urological procedures. Simple procedures normally undertaken under local anaesthetic in adult patients may require general anaesthesia in children. Respite care is sometimes needed for families with children requiring dialysis.

Additional measures of outcome for auditing in children are:

- Rate of increase in height
- Growth of head circumference
- Number receiving enteral feeds
- Number receiving growth hormone
- Developmental assessment
- Psychosocial development
- Progression in puberty
- Post-transplant: number of children on alternate day steroid therapy

6.11 Recommended calorie and protein intakes per kilogram are greater the younger the child:

Age (months)	Energy (kcal/kg)	Protein (g/kg)
0–3	115–150	2.1
4–6	100–130	1.6
7–12	95–125	1.5
12–36	95–125	1.1
36–72	1460–1810/day	1.1
72–120	1680–2040/day	28.3 g/day

From: Department of Health report on health and social subjects no.41. *Dietary reference values for food, energy and nutrients for the UK.* HMSO, 1991.

6.13 See 5.39 in this list.

6.20–6.26 Transperitoneal solute transport is similar in children and adults, though there is some controversy about the correct method of normalising the results for differences in body size. As with haemodialysis, no optimum weekly *Kt/V* or creatinine clearance has been established for child patients, but they should not be less than those used for adults.

Ultrafiltration is more difficult to achieve in children because of greater lymphatic absorption and mass transfer of protein, and the more rapid glucose absorption from the peritoneum in children compared with adults. For these reasons short dwell CCPD is more often the preferred method in children.

6.33 See 5.53 in this list.

7.10 Donation of parental kidneys is becoming more common, and should be encouraged [Kohaut and Tejani 1996].

7.16 There is a need for specialist paediatric urological input because of the frequent association of ESRF with congenital disorders of the lower urinary tract.

7.28 As is the policy with the UKTSSA, kidneys from child donors should be preferentially offered to children. Because of the small recipient pool, beneficial matches are less commonly obtained in children.

7.43 See 5.53 in this list.

7.50 Pre-emptive transplantation is more common in children than adults, in order to attain optimal growth and development.

7.54 Age affects transplant survival as there is an increased incidence of technical difficulties in those aged <1 year; 5-year graft survival is 52% in those <5 years old, 58% in 5–9 year olds and 60% in 10–15 year olds. Overall graft survival after 10 years in

those transplanted in 1980–1982 was 29% [European Renal Association 1996]. Transplantation is the preferred management of ESRF when a weight of 10 kg has been achieved by the patient.

8.3 The incidence of acute renal failure in children is 7.5 pmp per year. In 68% of cases this is due to the haemolytic-uraemic syndrome.

8.12 Most children with acute renal failure are dialysed using automated peritoneal dialysis machines. Haemodialysis is used if plasma exchange is indicated. Continuous veno-venous haemofiltration or haemodialysis is used in multisystem failure.

8.15 & 8.16 The management of children in acute renal failure requires the special skills and cooperation of paediatric or neonatal intensive care units, with in-house paediatric nephrologists.

8.23 Audit the number of children treated with plasma exchange

9.2 A GFR of <25 ml/min/1.73 m^2, which corresponds to a plasma creatinine of about 150 µmol/l in a 5 year old child, merits referral to a specialised unit. The prevalence of chronic renal failure was 53 pmcp on 31 December 1992. The national acceptance rate of 4.2 pmp per year in the UK represents 240 new patients. These children should be managed in specialised nephrology centres or where there is a system of shared care with a paediatric nephrologist.

9.5 See 5.37 in this list.

9.7–9.9 See 6.11 in this list.

10.1 Children with urinary tract infections should be investigated. Those with bilateral scarring need to be reviewed by a paediatric nephrologist [Dudley and Chambers 1996].

10.4 Liaison with urologists is vital in paediatric nephrology, in which nephrology and urology should be regarded as different aspects of the same discipline, much as cardiology and cardiac surgery are linked.

12.1 Quality of life assessment should be extended to the family of a child with renal failure as well as to the child; parents may carry an exceptionally heavy burden.

A1.1 Renal failure is much less common in children than in adults, but its management requires special expertise both psychosocial and medical. Therefore children requiring treatment are best aggregated in a few specialist centres.

A1.4 Slowing of growth is often present in chronic renal failure.

A1.7 (iv) Congenital abnormalities of the bladder and lower urinary tract may cause obstruction, and are a frequent cause of renal failure.

A1.7 (vi) The time at which a young patient is ready to transfer to an adult unit is dependent upon his or her maturity (both physical and psychological) as well as age. Links with an identified adult nephrologist should be encouraged to enable satisfactory handover and further collection of data such as long term morbidity and mortality, or achievement of final height. Expertise should be available to deal with problems specific to or common in adolescence such as rebellion, further education, leaving home and sexual difficulties.

Appendix 3

Summary of possible items for audit

Audit is mandatory for demonstrating the quality of care given and for guiding further improvement. To be effective, a wide range of quality outcomes must be measured frequently and compared between institutions. Comparative audit using agreed standardised formats for the exchange of data will create aggregate databases. We recommend that audit initiatives be concentrated on measurement of outcomes and on processes that have a proven role in determining morbidity and mortality in patients with end stage renal failure.

Haemodialysis

A3.1 The following is a list of items for which data can be obtained in order to carry out audits of patients on haemodialysis.

- ***Demographic data***

  Age distribution of patients receiving haemodialysis

  Numbers on home haemodialysis vs centre haemodialysis

  Numbers on thrice vs twice weekly dialysis

- ***Technique: numbers of patients using***

  Bicarbonate vs acetate dialysis

  Cellulosic vs synthetic membranes

  Standard dialysis vs high flux dialysis vs haemofiltration

  Technique failure — number of patients transferred to CAPD

- ***Correction of anaemia***

  Percentage of patients receiving erythropoietin

  Haemoglobin frequency distribution (all patients)

  Percentage of patients with Hb <10 g/dl

- ***Dialysis adequacy and nutrition***

  (see Appendix 4 for methodology and further discussion)

  Kt/V or URR frequency distribution in dialysis population

  Assessed dietary protein intake (DPI) frequency distribution

  OR

UKM assessed protein catabolic rate frequency distribution

Pre-dialysis serum bicarbonate frequency distribution

Pre-dialysis serum albumin frequency distribution

- ***Blood pressure control***

Systolic, diastolic and mean arterial pressure (MAP) frequency distribution

- ***Cardiovascular disease***

Presence of myocardial disease (see end of Appendix 4)

Presence of peripheral vascular disease (see end of Appendix 4)

Plasma cholesterol, HDL, LDL and triglycerides

Whether it is useful to measure and/or treat raised plasma cholesterol and triglyceride concentrations in dialysis patients has not yet been tested by controlled trial. Until this information becomes available, fasting plasma cholesterol, HDL, LDL and triglycerides should be measured at least annually to allow correlation with cardiovascular disease and outcome.

- ***Biochemical profiles***

Pre-dialysis: potassium, calcium, phosphate, bicarbonate, serum albumin, and iPTH frequency distribution

- ***Transmissible disease***

Prevalence of hepatitis B surface antigen positive patients

Prevalence of hepatitis C (antigen*) positive patients

Prevalence of HIV positive patients

* Hepatitis C antigen is normally sought only in patients with hepatitis C antibody.

- ***Hospitalisation***

The number of admissions to hospital and the mortality rate are crude markers of the general health of a population of dialysis patients. This information is only meaningful if the population is clearly defined and account is taken of comorbidity factors.

Mean admissions to hospital per patient per year

Mean days spent in hospital per patient per year

(Both calculated for patients <90 and >90 days on dialysis)

- ***Water quality***

Bacterial counts and endotoxin levels: test frequency and results

■ ***Access for dialysis***

No standards can be set at the moment for dialysis access, which is influenced strongly by the case-mix of patients (eg proportion of diabetics and elderly patients with vasculopathy), but we recommend the following items for audit:

First access

Timing of access in relation to start of dialysis

Proportion of primary access by:

radiocephalic or brachiocephalic A-V fistula

PTFE or other prosthetic fistula

central venous line or similar access (eg Permacath^{TM})

Success rate of first attempt at production of access (target >90%)

Duration of function of first access procedure

Cross-sectional audit of maintenance access

Proportion of patients on haemodialysis treatment using:

radiocephalic or brachiocephalic A-V fistula

PTFE or other prosthetic fistula

central venous line or similar access (eg Permacath^{TM})

Number of inpatient days related to access problems (clotting, infection etc)

■ ***Outcome***

Patient survival (see A3.8) in those aged 18–55 years at onset with standard primary renal disease (ERA codes 0–49) and in those with diabetes

Peritoneal dialysis

A3.2 Possible items for audit of peritoneal dialysis are included in the following list.

■ ***Demographic data***

Age distribution of patients receiving peritoneal dialysis

■ ***Technique***

Number of patients on disconnect systems

Numbers on CAPD, APD

Immediate catheter non-function/leak

Catheter survival rate

- ***Correction of anaemia***

  As for haemodialysis (above)

- ***Dialysis adequacy and nutrition***

  (see Appendix 4 for details of methodology and further discussion)

  Assessed dietary protein intake frequency distribution

  Kt/V; weekly creatinine clearance

  Serum albumin

  Skinfold thickness and mid-arm circumference

- ***Correction of biochemical parameters***

  Serum potassium frequency distribution

  Serum bicarbonate frequency distribution

  Serum albumin frequency distribution

- ***Blood pressure control***

  As for haemodialysis (above)

- ***Cardiovascular disease***

  As for haemodialysis (above)

- ***Transmissible disease***

  As for haemodialysis (above) (see Chapter 11)

- ***Peritonitis***

  Peritonitis rate — episodes/patient-month of therapy

  Primary cure rate — % (without need to remove catheter)

  Culture negative rate — %

- ***Exit site infections***

  Rate — episodes/patient-month of therapy

- ***Hospitalisation***

  As for haemodialysis (above)

■ ***Temporary transfer (<2 months duration) to haemodialysis***

Number and rate

■ ***Outcome***

See A3.8 below

Transplantation

A3.3 The following list contains items that can be subjected to audit before and after renal transplantation.

■ ***Pre-transplant***

Number of organ donors each year/million population

Number of renal transplants performed per million population per annum, both cadaver and living, related and unrelated

Proportion of patients on dialysis entered on to the transplantation waiting list

Waiting time of patients on dialysis

Equity of access to: (a) the transplant waiting list; (b) transplanted kidneys (Particular attention should be paid to patients from ethnic minorities and older patients, and the age range on the transplant waiting list should be reviewed.)

Number of patients on the transplant waiting list and their degree of sensitisation against common HLA antigens (see Appendix 4)

Proportion of patients receiving a 'beneficial match' kidney

Number of kidneys that are unsuitable for use because of their anatomy or damage during retrieval

■ ***Early (first year) post-transplant***

Cold storage times of transplanted kidneys

Proportion of cadaver transplant recipients with immediate function, delayed function and failure of function

Number of days of hospitalisation in the first and subsequent years after transplantation

Proportion of patients with urological problems after grafting

Proportion of patients with renal vascular problems after grafting

Incidence of wound infections after transplantation

Number of other serious infections (abscesses, septicaemia, serious fungal or viral disease) in the post-operative period and later

Proportion of patients with one or more histologically diagnosed rejection episodes in the first 3 months

Percentage of these episodes that were resistant to corticosteroid treatment

Incidence of graft loss from acute rejection in the first 3 months

Plasma creatinine concentration in those with functioning grafts

Incidence of death with a functioning graft in the first 3 months

■ ***Long term post-transplant***

Frequency and causes of death

Frequency and attributed causes of graft failure

Plasma creatinine concentration in those with functioning grafts

Prevalence of hypertension requiring treatment

Prevalence of cardiovascular events and disease (see Appendix 4)

Plasma cholesterol (Whether it is useful to measure and/or treat raised plasma cholesterol concentrations post-transplant remains controversial. Until the results of long term controlled trials are available, plasma cholesterol should be measured annually to allow correlation with outcome.)

Prevalence of malignant disease of all types, including skin cancers

Number of pregnancies, spontaneous and therapeutic abortion rates and complications of pregnancy (eg Caesarian section rate)

Acute renal failure

A3.4 For audit of acute renal failure the following data should be recorded:

Number of patients requiring temporary renal support for ARF

Causes of the acute uraemia (including how many were in fact acute-on-chronic renal failure, ie requiring dialysis at 90 days)

Number of organ systems failing and APACHE II (Acute Physiological and Chronic Health Evaluation) score at admission, start of dialysis and day 7

Site of management

Technique of renal replacement therapy used

Outcome: percentage leaving the ICU alive
with renal function
remaining in need of dialysis support

percentage discharged from hospital

percentage surviving 6 or 12 months after onset

Chronic renal failure

A3.5 Audit of patients in chronic renal failure should include collection of the following data:

■ ***Patients joining the low clearance clinic***

Serum creatinine at time of first referral

Number requiring immediate dialysis

■ ***Patients attending the low clearance clinic***

Distribution and % of patients achieving target levels for:

blood pressure

serum calcium, phosphate and bicarbonate

serum iPTH

General nephrology

A3.6 The following points can be used for audit of renal biopsy:

Number of renal biopsies done per year

Number of individuals performing biopsy during the period of analysis

Success rate in obtaining adequate tissue (>10 glomeruli/section) at first attempt

Clinical complication rate and nature (bleeding, symptomatic A-V aneurysm etc) in uraemic and non-uraemic subjects

Microbiology

A3.7 Number of patients positive for hepatitis B, hepatitis C and HIV on dialysis or following transplantation.

Survival

A3.8 We take the view that the most important outcome statistic is the survival rate of individual patients taken on for treatment of end stage renal failure, whatever treatment they may receive first, or subsequently.

Survival is influenced greatly by age and comorbidity, especially diabetes mellitus and cardiovascular disease, as discussed in Appendix 4 (A4.7), but remarkably little by method of treatment selected (see below). Gender does not seem to be a major determinant of outcome in end stage renal disease. Overall national and international survival data are available from the register of the European Renal Association [Brunner *et al* 1988], by age [Valderrábano *et al* 1995] and by comorbidity [Khan *et al* 1996]. However, complete data on outcomes of patients of all ages, with and without comorbidity, are lacking for the United Kingdom; during the period analysed, the return of data from the UK to the ERA Registry fell from 85% to approximately 65%, so detailed outcome standards cannot be set until more complete national data have been collected by the National Renal Registry.

However, provisional information has been kindly donated by the ERA Registry for patients aged 18–55 with 'standard' primary renal diseases (ie non-systemic diseases, ERA data codes 0–49), and for all primary renal disease codes except diabetes mellitus (ERA data codes 80/81), for the UK. Both sets are available for: (a) all patients entering treatment for end stage renal disease from 1984 to 1993 for whom the outcome was death; (b) the subset of those treated initially with haemodialysis censored if they depart from that treatment; (c) the subset of those treated initially with peritoneal dialysis censored if they depart from that treatment.

The figures for mean percentage survival of patients aged 18–55 years are as follows:

	Standard primary renal disease			All diseases except diabetes		
		First treatment			First treatment	
	All*	HD	CAPD	All*	HD	CAPD
1 year	95.7	95.1	97.0	93.7	92.8	95.6
5 years	84.4	83.3	86.4	80.1	79.0	82.7
10 years	73.6	72.5	75.9	66.4	64.5	72.5
n =	5131	2981	1621	7290	4275	2245

* Including patients following transplantation, or transplanted for a period of time returning to dialysis

It should be noted that this analysis takes no account of the presence or absence of comorbidity (see Appendix 4), which may vary in different parts of the UK, particularly cardiovascular disease. It does however allow for effects of age, diabetes mellitus and other systemic diseases potentially affecting organs besides the kidney. Clearly treatment modality makes little difference to survival in the 18–55 year old group. In addition, the figures are very similar to those for patients of all ages (but predominantly under 60 years of age) transplanted, as shown in the UKTSSA data (see Chapter 7). Thus single provisional targets can be set for patient survival at different intervals following the start of treatment for end stage renal failure, independent of treatment received:

Recommendation

The following provisional targets may be set for mean survival:

For all patients with 'standard' primary disease aged 18–55 years
1 year >90%; 5 years >80%; 10 years >70%

For all patients except those with diabetes mellitus aged 18–55 years
1 year >90%; 5 years >75%; 10 years >65%

It is hoped that, as data from the National Renal Registry accumulate, it will be possible to extend these targets to older patients, and to stratify them for comorbidity.

Appendix 4

Methodology

Data collection and expression

A4.1 No standards can be set unless data are available to find out what is and can be achieved; this topic is discussed in Chapter 1 (1.8–1.14, 1.19). Then the performance of an individual, or an individual unit, can be judged against what is being achieved elsewhere. There are different ways in which this can be done: minimum, average and optimum (target) standards all can be set and used.

The data collected for setting standards and for audit can be *discontinuous* or *continuous* — yes/no or continuously variable. Examples of a discontinuous variable are alive/dead, transplanted kidney working/not working, or a scoring system for quality of life or morbidity. Examples of a continuous variable are the concentration of haemoglobin or of albumin in the blood, or some measure of the amount of dialysis received.

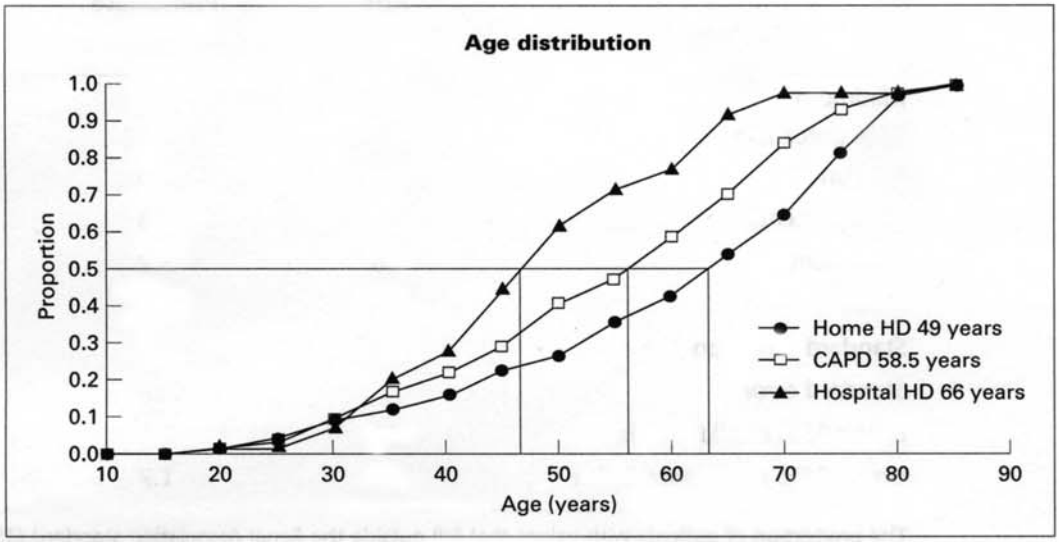
Obviously the way in which these various types of data should be presented and used to set standards and to conduct audit will be different.

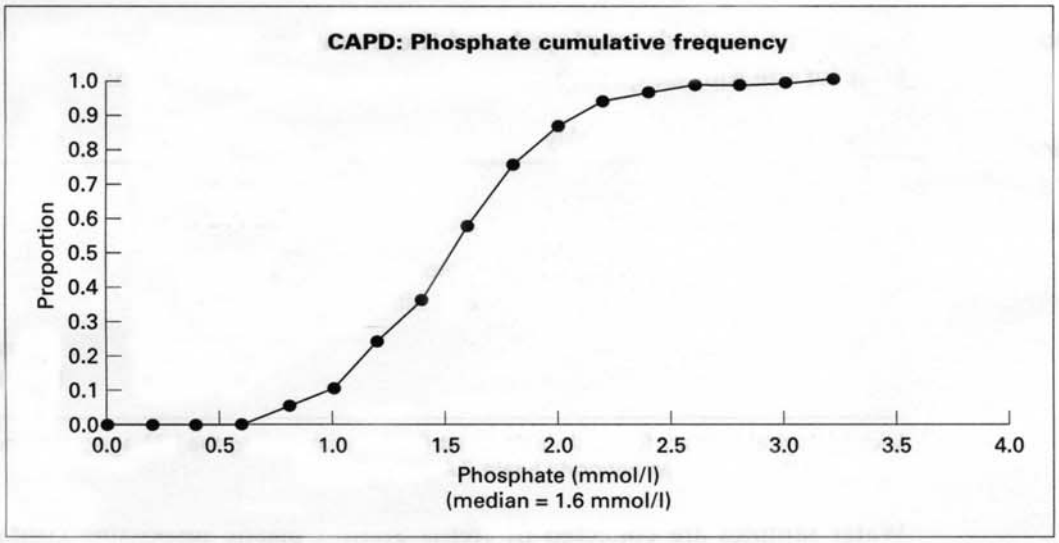
Discontinuous data

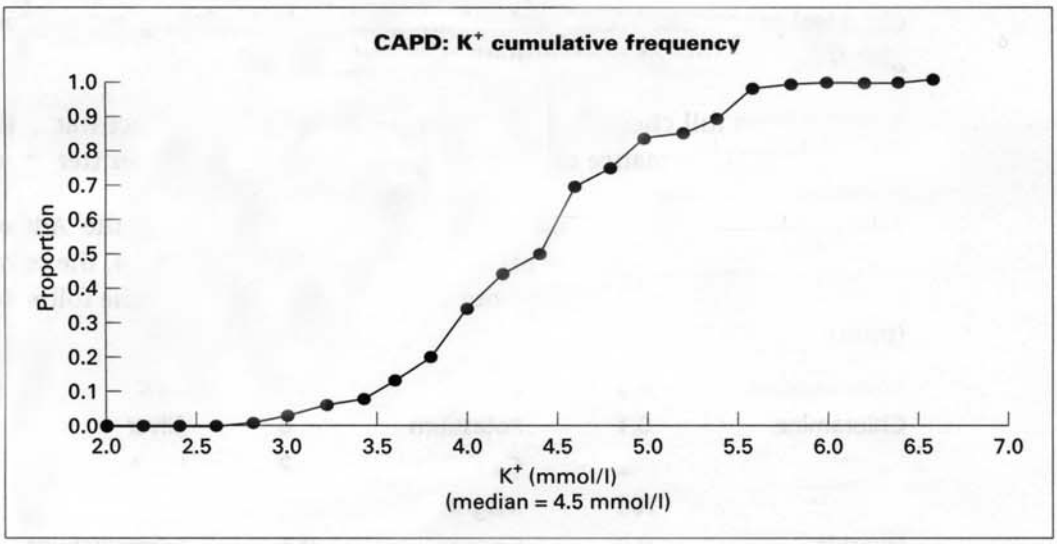
There is little difficulty in understanding whether a patient has survived or not, but in setting standards it is important to realise that any data upon which **recommended standards** are set have a statistical variability. For categorical data to which a yes/no question may be asked, the appropriate statistic is the chi-squared test or some variation of this. In Chapter 7 the standards achieved in the United Kingdom for survival of patients on dialysis or following transplantation and of transplanted kidneys have a mean (average) but also a variability about that average, usually expressed as the *standard deviation*: 1 standard deviation either side of the mean encompasses about two-thirds of the observations. One way of expressing whether or not (for example) a cumulative survival rate in a particular unit differs from the recommended standard is to set a standard based upon the number of standard deviations by which the rate differs from the mean of that achieved in the country as a whole. (This has been declared dubious by the UKTSSA statisticians!)

Continuous data

These are best displayed and analysed as a *continuous cumulative variable plot*. As an example of the use of this simple method of display, data are presented in graphical form for CAPD patients in an English unit during 1994 which were shown to purchasers. These data are also shown expressed as percentages or as absolute numbers in a table


Age distribution
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
10
20
30
40
50
60
70
80
90
Age (years)
Home HD 49 years
CAPD 58.5 years
Hospital HD 66 years


CAPD: Phosphate cumulative frequency
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Phosphate (mmol/l)
(median = 1.6 mmol/l)


CAPD: K+ cumulative frequency
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
K+ (mmol/l)
(median = 4.5 mmol/l)

Number of values	Age 122	Phosphate 122	Potassium 122
Minimum	23	0.7	2.5
25% percentile	46	1.3	4.0
Median	58	1.6	4.5
75% percentile	69	1.8	4.9
Maximum	86	3.2	6.7
Mean	56	1.6	4.4
Standard deviation	15	0.4	0.7
Standard error	1	0.04	0.06
Lower 95% confidence index	53	1.5	4.3
Upper 95% confidence index	59	1.7	4.5

The proportion of patients with values that fell outside the Renal Association standard (1997) was 59% for phosphate and 2% for potassium.

Laboratory testing

A4.2 The methods employed, and the frequency of sampling, at the Lister Renal Unit for the routine quality monitoring of water are as follows:

Water for dialysis and test schedules

	Weekly	Monthly	3-monthly	6-monthly
Plant supply		Chlorine and nitrates	Full chemical analysis	
Plant product	TVC, Eu	Chlorine and nitrates	Full chemical analysis	
Dialysis machines			Dialysis fluid TVC, Eu	Dialysate Na, HCO_3, K, Ca

Microbiological tests are for total viable count (TVC) incorporating the R2A agar, and endotoxin units (Eu) using the Limulus amoebocyte lysate (LAL) gel clot test

Water samples are collected in sterile Sterilin plastic disposable containers using aseptic techniques. These samples are tested both for microbiological quality and for chemical properties. Weekly microbiological analysis of the plant product water can give early warning of contamination of dialysis fluid.

Simultaneous full chemical analysis of both plant and product water allows assessment of the performance of different components of the water treatment plant.

According to the limits laid down by the Association for the Advancement of Medical Instrumentation the pH should be in the range 6.0–7.4, the refractive index ca 1.333, and impurities should not be present in more than the following amounts (ppm):

Total chlorine	0.5	Sodium	70	Zinc	0.1
Chloramine	0.1	Potassium	8	Silver	0.005
Nitrate	2	Calcium	2	Lead	0.005
Sulphate	100	Magnesium	4	Aluminium	0.01
Fluoride	0.2	Copper	0.1	Formaldehyde	0

All samples are tested in accordance with standards laid down by the British and European Pharmacopoeia for environmental samples.

Culture of peritoneal dialysis fluid

Cooperation with the department of microbiology is essential if culture of peritoneal dialysis fluid is to be successful and useful. Concentrations of organisms in the fluid are low, many organisms are intracellular, and positive culture rates vary from 50% to over 90%. In the main document (6.31) we recommend that not more than 10% of cultures of apparently infected fluid should be negative. Guidelines for a technique of optimising cultures are given here, but it is important that clinicians and microbiologists ascertain the methods available, and develop a joint policy for the handling of specimens and methods of culturing them [British Society for Antimicrobial Chemotherapy 1987; Keane *et al* 1993].

- Inoculate PD effluent into blood culture media (10–50 ml) and culture aerobically and anaerobically.
- Concentrate up to 50 ml of effluent by centrifugation and re-suspend 1 ml of concentrate in nutrient broth or sterile saline. Inoculate blood and McConkey plates and observe growth for 72 hours, although 7 days is preferable. Cell lytic agents such as Triton X may be added prior to centrifugation to increase the yield of positive cultures.
- Semi-automated blood culture systems including Septi-check, BACTEC, Isolator and Signal systems are available; for many laboratories these may prove preferable and, although more expensive, save labour costs.
- Millipore filter culture is an effective means of isolating organisms but is technically difficult and fluids containing large numbers of cells and fibrin are cumbersome. This technique should be used primarily to look for fungi and acid-fast bacilli in patients with peritonitis refractory to conventional antimicrobial chemotherapy.
- Use of media with antiphagocytic substances such as polyanethol sulphonate and antibiotic-binding resins may increase the yield of positive cultures.
- Total white cell and differential cell counts on a non-centrifuged aliquot of PD effluent should be done by automated or standard haemocytometer counting chamber techniques.
- A Gram stain may be useful initially to detect organisms, but this is successful in only one-third of cases of CAPD peritonitis. When positive, however, its success in predicting the variety of organism is 85%.

Measurement of serum albumin

The concentration of albumin in the plasma is a surrogate measure for the nutritional health of the patient, and has been used to assess the overall quality of dialysis care; it correlates with outcomes. Unfortunately different methods of measuring albumin give different results. Immunochemical methods (eg nephelometry) in general give results that are lower than those employing dye binding, such as are used in multichannel analysers, and there is variation between different dye-binding methods. Therefore it is important both to give the method used when presenting any data and to establish values for the local normal population using this methodology [Blagg *et al* 1993].

Calculation of amount of haemodialysis delivered

A4.3 Contemporary quantification of dialysis depends on calculations all of which relate to the cyclic variation in blood urea concentrations that patients undertaking regular haemodialysis undergo: reduction in urea during dialysis, a 'rebound' period after dialysis arising from re-equilibration of urea throughout the body water, followed by the generation of urea from protein catabolism.

Blood sampling

Since all methods involving the measurement of small solute clearances in use at the moment depend upon the blood urea concentration in pre- and post-dialysis blood samples, it is crucial that these samples be taken in a standard fashion, and with great care.

The *post-dialysis* sample is of particular importance, since recirculation of already dialysed blood into the sample will falsely lower the measured blood urea, and thus overestimate the clearance. The method described by Priester Coary and Daugirdas [1997] can be recommended:

1 At the end of dialysis set the ultrafiltration rate to zero.

2 Reduce the blood flow to 50–100 ml/min.

3 Exactly 10 seconds after this blood flow reduction, STOP the blood pump; this time must not be exceeded since this would lead to an increase in the urea concentration in the sample drawn, owing to rebound.

4 Clamp the arterial fistula needle tubing and the arterial line upstream of the connection with the needle tubing.

5 Disconnect and draw blood from the fistula needle tubing. It is important to limit the amount of blood drawn, since a volume in excess of that in the tubing and needle (ca 3 ml) will lead to errors, as it will be mixed with blood from the fistula itself, which is again subject to rebound in urea concentrations.

6 After sampling, re-connect and proceed to wash back the extracorporeal circuit as usual.

This procedure samples blood at the end of dialysis before wash-back and the urea rebound. The exact timing of the post-dialysis sample is important, and becomes crucial when high blood flow, short dialysis methods using high flux membranes are in use. In a steady state the urea in the body can be considered as a single pool (see below); this assumption does not hold true in the non-steady state during dialysis, and immediately after dialysis when there is a rapid rebound in blood urea before the steady slow increment dependent upon urea generation is established.

This rebound arises almost entirely from: (a) diffusion of urea from poorly perfused volumes of body water, some extracellular but most within the cells [Tattersall *et al* 1998]; this is only complete after 30–45 minutes; (b) a more rapid (2 min) equilibration of the cardiopulmonary circulation [Schneditz *et al* 1992]. The rebound is most pronounced when dialysis is short and efficient.

Ideally, therefore, after rapid dialysis the post-dialysis sample *should* be taken 30–35 minutes after the end of dialysis, but in practice this is inconvenient or impossible.

Therefore measures must be taken to estimate this post-rebound plasma urea by calculations some of which depend on measuring intradialytic sample(s) (see below).

The *pre-dialysis sample* must not be contaminated by infused saline or saline in the syringe. Ideally it should be taken into an empty syringe bearing the dialysis needle; if not, saline must be cleared from the line before sampling. Blood samples must be sent for analysis quickly so that potassium, bicarbonate and phosphate can be measured on rapidly separated plasma, and the laboratory should be asked to measure pre- and post-dialysis samples for urea in the same batch to avoid interbatch variation.

Urea reduction ratio

An approximate measure of dialysis delivered is provided by the simple calculation of the *urea reduction ratio* (URR) [Lowrie and Lew 1990, 1991]. This is calculated from the urea concentration in samples taken before (C_0) and after (C_t) dialysis:

$$URR = 100 \times (1 - C_t/C_0)$$

Good correlations have been obtained between measurement of the URR and *Kt/V* [Lowrie and Lew 1991], and both are predictive of outcome of dialysis treatment [Owen *et al* 1993]. However, the confidence limits are wide, and the relationship is curvilinear, URR underestimating *Kt/V* at both high and low clearances, and overestimating it in the middle range. Thus it has been criticised as a method of quantification in individual patients [Depner 1993; de Oreo and Hamburger 1995], principally because it ignores urea generation during dialysis and assumes that its distribution volume remains constant.

Urea kinetic modelling

The calculation of *Kt/V* has become the current standard for calculating delivery of haemodialysis [Depner 1991]; however, as noted in the main text, there are many theoretical and practical problems with its calculation and application.

Assuming a constant volume of distribution, the concentration of urea at any time (C_t) may be described by the general equation:

$$C_t = C_0.e^{-Kt/V}$$

which can be rearranged in the form:

$$Kt/V = \ln(C_0/C_t)$$

In *Kt/V*, which is a dimensionless parameter:

- K = urea clearance of the dialyser (ml/min)
- t = duration of dialysis (min)
- V = volume of urea distribution (ml)

It is possible to calculate V from height and/or body weight (see below) but it is normally a virtual or assumed quantity. *Kt/V* has the major advantage over URR that if it is regarded as too low for the patient's requirements the desired increase in K or/and t can be calculated and appropriate action taken.

More complex derivations of Kt/V

Whilst this simple formula for *Kt/V* delivers the greater proportion of information that more complex and refined analyses discussed below can provide, its usefulness decreases with some modern dialysis techniques, especially short, high blood flow rate, high flux dialysis, in which the validity of the approximation inherent in these calculations — that there is only a single exchangeable pool of urea within the body — diminishes, with an increased rebound of blood urea immediately after the end of dialysis. It ignores also the additional component of *K* arising from the patient's own residual renal function, which becomes more important with early start dialysis and in patients who maintain appreciable residual function.

In addition, *urea generation* during the dialysis opposes the fall in blood urea concentration brought about by clearance through the dialyser. As an extreme example, continuous dialysis as used for acute renal failure treatments will show a URR and *Kt/V* of zero, even if dialyser clearance may be very high. The effects of urea generation during dialysis and *rebound in urea concentration* post-dialysis on *Kt/V* oppose each other, and fortunately balance each other out approximately during a 4-hour dialysis, which thus remains a useful one in these circumstances. However, for *longer dialyses*, *Kt/V* will be UNDERestimated because rebound is less and generation greater, whilst with *shorter dialyses Kt/V* will be OVERestimated. These effects are not small; calculated by the simple $\ln(C_0 - C_t)$ method, the *Kt/V* of a 2-hour dialysis and an 8-hour dialysis may be the same, but the 'true' *Kt/V* of the longer dialysis is 42% greater.

Urea lost in the ultrafiltrate is not accounted for by the simple model, resulting in an UNDERestimate of *Kt/V*. This convective urea clearance is greater the greater the ultrafiltrate volume, and is thus of particular importance in high flux dialysis.

Calculating URR or *Kt/V* in the simple way also ignores the patient's own *residual renal function*. This may be considerable if the patient is taken early on to dialysis to avoid morbidity (see Chapter 9), and normally decreases with time on dialysis, so it contributes a diminishing amount to the patient's overall urea and other solute clearance.

A value for the *dialyser clearance* at the patient's blood flow rate is used in many computer packages (eg Medical Devices Agency evaluation 245, 1995) to calculate *Kt/V*. However, *K* is not always known precisely for the dialyser being used, and may differ in *in vitro* testing from *in vivo* use by as much as 20% [Zehnder and Blumberg 1994]. This effect arises in part from effects of haematocrit on dialyser performance, ultrafiltration as just discussed, and access recirculation [Hoenich *et al* 1993].

A more rigorous and more generally applicable approach to kinetic modelling requires, therefore, knowledge not only of the pre- and post-dialysis blood urea but of the next pre-dialysis urea, the dialyser clearance, the patient's residual renal function, the interdialytic interval, amount of ultrafiltration and some correction for urea generation and rebound. Whilst the calculations can be done simply by entering the data and using computer programmes, the burden of the data collection itself for this more complete type of analysis becomes greater.

The Gotch equation

The original mathematical analysis of solute removal by dialysis was performed by Wolf *et al* [1951]. The introduction of the parameter *Kt/V* for urea as a measure of low molecular weight solute clearance by Gotch and Sargent [1985] had a major influence and has formed the basis for most of the work done since. Their method used a figure for the *in vitro* dialyser clearance (which has just been criticised above), C_0 and C_t, and also the pre-dialysis blood urea at the next dialysis C_{02} and the inter-dialytic interval t_{in}. Using these data, and an iterative computer programme, V and the urea generation rate between dialyses, G, were solved, and *Kt/V* calculated. G is important since G/V is a measure of urea generation and hence of protein breakdown (protein catabolic rate, PCR), which can be derived from this urea nitrogen appearance rate (nPCR = 149.4 G/V + 0.17).

Modified approximations for calculating Kt/V

As a result of the inadequacies of the simplest formula, and the complexity of full analysis, at least 10 'short cut' methods to calculate *Kt/V* have been suggested [Jindal *et al* 1987; Basile *et al* 1990], that of Daugirdas [1993] being particularly popular; see Movilli [1996] for review. Of these modified approximations, only the Daugirdas formula requires input other than C_0 and C_t; it uses in addition the ultrafiltration volume V_{uf} and the body weight at the end of dialysis, W_t, thus adding a measure of convective loss and a function of V:

$$Kt/V = \ln(C_t/C_0 - 0.0081) + (4 - 3.5C_t/C_0).V_{uf}/W_t$$

Whilst generally useful and an improvement on the simplest formula, it ignores urea rebound and thus may overestimate clearance.

Unfortunately all the 'short cut' methods give different values for *Kt/V* from the same data input [Movilli 1996], which means that if real accuracy is required, and urea generation rates and hence nitrogen catabolism are to be calculated, a formal calculation of this parameter with all the extra data input will be required.

Precise calculation of Kt/V

This needs no value for dialyser K and can be solved without iteration [Tattersall *et al* 1996, 1998]. V can be calculated from the Watson equation [Watson e*t al* 1980], but Wong *et al* [1995] have pointed out that the best correlation with the deuterium labelled water space is the simple assumption that 58% of body weight is water. The analysis, although the basis is complex, can be performed simply using a computer programme into which the following data are entered:

Input data required

- *The patient*

W_t = post-dialysis body weight (kg)

Calculate V as 58% of body weight in kg [Wong *et al* 1995]

OR

A = age (years); H = height (cm)

and use the Watson *et al* [1980] formula:

For males: $V = 2.447 - 0.09156A + 0.1074H + 0.3362W_t$

For females: $V = -2.097 + 0.1069H + 0.2466W_t$

- *The dialysis*

C_0 = pre-dialysis urea (mmol/l)

C_t = post-dialysis urea (mmol/l)

(both taken as described above)

V_{uf} = ultrafiltration volume (pre-dialysis weight – W_t)

t = dialysis time (min)

n_d = number of dialyses per week
(normally three, but see below for twice weekly dialysis)

t_{in1}, t_{in2}, t_{in3} = interdialytic times (min)

If the patient is dialysing three times a week on Monday, Wednesday and Friday, and the measurements are made on a Monday, these times will be 1440, 1440 and 2880 min respectively; 1440, 2880 and 1440 min if the measurements are made on a Wednesday, and so forth.

C_{02} = pre-dialysis urea before dialysis following C_t (mmol/l)

C_{eq} = post-rebound blood urea 45 min post-dialysis (mmol/l)

These two parameters *can* be measured, but this requires organisation and, in the case of C_{eq}, that the patient should wait for a venepuncture. Alternatively, if the patient is in nitrogen balance they can be calculated.

Calculation of the post-rebound urea concentration [Smye *et al* 1994; Tattersall *et al* 1996, 1998]. This can be done to within 0.3 mmol using a mathematical approximation to a two-pool model. The '35' in the equation represents the time in minutes taken to clear all peripheral body compartments. This includes the value of cardiopulmonary recirculation [Schneditz *et al* 1992] which is complete in 2 minutes. If there is access recirculation, the rebound will be underestimated by this method:

$$C_{eq} = C_0 \times \left(\frac{C_t}{C_0}\right)^{t/(t+35)}$$

Calculation of urea concentration before the next dialysis. Because dialyses are not performed at regular intervals, C_{02} may not be the same as C_0:

$$C_{02} = C_0 \left[\frac{t_{in1}\left[1 - \left(\frac{C_{eq}}{C_t}\right)^3\right]}{t_{in1}\left(\frac{C_{eq}}{C_t}\right)^2 + t_{in2}\left(\frac{C_{eq}}{C_t}\right) + t_{in3}} + \frac{C_{eq}}{C_t} \right]$$

■ *The urine* (if the patient has residual renal function)*

V_u = interdialytic urine volume (litres)

C_u = interdialytic urine urea concentration (mmol/l)

* The patient should void immediately after dialysis finishes, and discard this urine, voiding again at the beginning of the next dialysis.

Then the intradialytic urinary urea clearance (K_{ru}) can be calculated:

$$K_{ru} = \frac{2V_u C_u}{(C_{02} + C_{eq})t_{in1}}$$

Finally, the *Kt/V* can be calculated from the natural logarithm ($\log_e$ or ln) of the ratio of blood urea concentration to that 45 minutes post-dialysis, as before *but corrected for urea generation, ultrafiltration and residual renal function* [Tattersall *et al* 1998]:

$$Kt/V = \ln\left(\frac{C_0}{C_{eq}}\right) + \ln\left[\frac{1}{1 - \frac{t}{t_{in1}}\left(\frac{C_{02}}{C_{eq}} - 1\right)}\right] + \ln\left(\frac{V + V_{uf}}{V}\right) + \ln\left(\frac{1}{1 - \frac{K_{ru} \times 10080}{V \times n_d}}\right)$$

Urea generation | Ultrafiltration | Renal function

There remain theoretical pitfalls even using the full calculation just outlined. However, it provides a more precise measure of clearance from both dialyser and kidneys (*Kt/V*), and in particular allows precise calculation of what readjustments are necessary in the dialysis prescription if the *Kt/V* is found to be inadequate.

Nitrogen generation rate (protein catabolic rate, PCR)

Another advantage of kinetic modelling already noted is that an approximation to protein breakdown (nPCR in g protein catabolised/kg ideal wt/24 h) can be derived from the urea generation rate *G* (mmol/min), which in turn is derived from C_t, C_{02} and t_{in}. In the absence of fluid accumulation and renal excretion, the slope of the rise in blood urea in the interdialytic interval is:

$$\frac{G}{V} = \frac{C_{02} - C_t}{t_{in}}$$

Since fat contains very little water, the ideal body weight can be related to *V* and nPCR to *G/V* thus:

$$\text{nPCR} = \frac{G}{V} \times 149.7 + 0.17$$

The value 0.17 represents obligatory non-urea nitrogen losses and is included only to make nPCR compatible with dietary protein intake (DPI).

Thus the full equation for nPCR is:

$$\text{nPCR} = \left[\frac{C_{02} - C_{eq}}{t_{in1}} + \frac{\left(K_{ru} + \frac{V_{uf}}{t_{in3}} \right) \times \text{TAC}}{V} \right] \times 149.7 + 0.17$$

However, there are a number of caveats about this calculation: the nPCR is only equivalent to DPI if the patient is in nitrogen balance and there is no unusual non-urea nitrogen loss (eg massive proteinuria), and it ignores post-dialysis rebound of urea, urea generation during dialysis and urea ultrafiltered during dialysis.

Also, this equation contains a term not discussed hitherto but which was used by Gotch and Sargent in their original analysis: TAC, or the weekly time-averaged urea concentration $(1/T)C(t)\mathrm{d}t$ expressed in mmol/l, which is required if there is residual renal function. It can be derived from:

$$\text{TAC} = \frac{C_0 t_{in3} + \frac{C_{02} C_{eq} t_{in2}}{C_0} + (C_{02} + C_{eq}) \frac{t_{in1}}{2} + \frac{C_{02} - C_{eq}}{2t_{in1}} \left({t_{in2}}^2 - {t_{in3}}^2 \right)}{t_{in1} + t_{in2} + t_{in3}}$$

Twice weekly dialysis

All the above applies only to thrice weekly dialysis, which the main body of this document recommends as standard. We recognise that some patients will be receiving twice weekly (×2/w) dialysis, which is corrected for by the term n_d in the residual renal function part of the *Kt/V* equation above. TAC and C_{02} will need to be calculated differently, however, if an estimate of nPCR is required:

$$\text{TAC} = \frac{(C_{02} + C_{eq}) \frac{t_{in1}}{2} + \frac{C_{02} - C_{eq}}{2t_{in1}} {t_{in2}}^2}{t_{in1} + t_{in2}} \times 2/\text{w} \qquad C_{02} = C_0 \left[\frac{t_{in1} \left[1 - \left(\frac{C_{eq}}{C_t} \right)^2 \right]}{t_{in1} \left(\frac{C_{eq}}{C_t} \right) + t_{in2}} + \frac{C_{eq}}{C_t} \right] \times 2/\text{w}$$

Calculation of amount of peritoneal dialysis delivered

Measurement of Kt/V urea for CAPD

A4.4 As noted in the main body of the text, there is no standard accepted and validated method of quantifying peritoneal dialysis [Kopple *et al* 1995b; Robertson *et al* 1995]. Obviously, as in patients receiving haemodialysis, *K* will be made up of a component resulting from dialysis and a component dependent upon residual renal function. In most patients the latter declines with time more slowly when receiving peritoneal dialysis than haemodialysis, so it forms a more important component in calculating *Kt/V* during the early years on continuous ambulatory peritoneal dialysis (CAPD). However, after 3–5 years residual renal function has

disappeared in all but very few patients on CAPD. Therefore, we must calculate *Kt/V* for both sources and aggregate them. Because CAPD is a continuous treatment, problems of short term equilibration are not as important as in haemodialysis.

It is possible to use a simple two-pool kinetic model for CAPD [Popovich *et al* 1979] in which one pool represents the peritoneal cavity and another the total distribution volume, and one can derive values for *Kt/V* urea and weekly creatinine clearances using this model [Robertson *et al* 1995].

Conventionally, however, in CAPD *Kt/V* is calculated in a non-kinetic fashion, and expressed on a weekly basis. If urine and dialysate are collected and urea or creatinine measured in these samples, then the component *Kt* can be established. The concentration in the blood for either parameter is assumed to be relatively constant, so a single sample may be analysed for blood urea or plasma creatinine concentration. If so wished, the urea concentration can be divided by 0.93 to correct for plasma water. The measurement of *V* can be, as for haemodialysis, either calculated using the formula of Watson *et al* [1980] or taken as 58% of body weight [Wong *et al* 1995].

Males: $V = 2.447 - 0.09156A + 0.1074H + 0.3362W$

Females: $V = -2.097 + 0.1069H + 0.2466W$ [Watson *et al* 1980]

where A = age (years); H = height (cm); W = body weight (kg)

OR

Assume V = 58% of body weight (kg) [Wong *et al* 1995]

Kt/V for the residual renal function is calculated from a timed sample of urine and a blood sample for urea determination, to give the urea clearance in ml/min; this is multiplied by the number of minutes in a week (7 × 1440), divided by *V*:

$$\text{Weekly } Kt/V \text{ (renal)} = \frac{C_{\text{urea}}(\text{ml/min}) \times 1440 \times 7}{V}$$

Kt/V for the peritoneal dialysis is calculated from the ratio of urea concentration in blood and dialysate, multiplied by the weekly volume of dialysate drained; this therefore includes convective losses of urea by ultrafiltration:

$$\text{Weekly } Kt/V \text{ (PD)} = \frac{(D_{\text{urea}}/P_{\text{urea}}) \times \text{Weekly drainage volume}}{V}$$

Then:

$$\text{Total weekly } Kt/V = Kt/V \text{ (renal)} + Kt/V \text{ (PD)}$$

Measurement of weekly creatinine clearance

The concept of using creatinine clearance to describe the quantity of peritoneal dialysis delivered can be traced back to the observations of Boen *et al* [1978] that 4–5 ml/min of clearance was required for health, whilst Twardowski and Nolph [1988] suggested a target of 40–50 litres/week normalising the clearance to 1.73 m^2. As with urea, the dialytic and renal components of the clearance must be measured to assess total clearance.

A problem then arises that, whilst urinary creatinine clearance can be measured easily, in patients with only residual renal function the secretion of creatinine is greatly increased by the raised plasma creatinine concentrations, so a falsely high estimate of glomerular filtration rate (GFR) is obtained from the creatinine clearance in these circumstances; see Cameron and Greger [1998] for discussion. It may, therefore, be more appropriate to use an estimate of GFR (see below) for residual renal function, and add this to the measured dialysis clearance of creatinine rather than the urinary creatinine clearance.

In CAPD patients creatinine clearance (urinary and dialysis creatinine clearance) conventionally has been expressed in litres/week, usually normalised to 1.73 m^2 body surface area [Twardowski and Nolph 1988] using the Dubois nomogram [Dubois and Dubois 1916]; 1 ml/min of true GFR equals 10.08 litres of creatinine clearance per week, so (for example) 60 litres/week is equivalent to 5.9 ml/min.

Residual renal creatinine clearance per week is measured as:

$$\text{Weekly } C_{cr}\,(\text{renal}) = \frac{C_{cr}(\text{ml/min}) \times 1440 \times 7}{1000} \text{ litres/week}$$

using a timed urine sample over a convenient period for urinary creatinine excretion; the period is not important provided its duration is known accurately. A single blood sample is taken for P_{cr}.

Dialysis creatinine clearance is measured as:

$$\text{Weekly } C_{cr}\,(\text{dialysis}) = \frac{D_{cr}V_{\text{dialysate}}\,(24\text{ h}) \times 7}{P_{cr}}$$

$$\text{Total weekly creatinine clearance} = C_{cr}\,(\text{renal}) + C_{cr}\,(\text{dialysis})$$

Protein catabolic rate in patients on CAPD

The normalised protein catabolic rate is often calculated for patients on CAPD in an attempt to assess nutritional status, but it should be noted that it has been criticised as at best a flawed marker of nutrition in CAPD patients [Harty *et al* 1994]; controversy continues on this issue.

The urea nitrogen appearance rate (G) is the net production or appearance of urea nitrogen in body fluids and all measurable outputs (urine, dialysate, faeces). Ignoring gastrointestinal losses (see below), *urea appearance rates* are given by simple measurements on timed samples of dialysate and urine:

$$G = \frac{D_{urea}V_{dialysate} + U_{urea}V_{urine}}{t} \quad \text{mg/min}$$

and empirically the PCR in g protein/24 h has been derived [Randerson *et al* 1981] from G as:

$$PCR = 10.76(G + 1.46)$$

This empirical relationship includes the fact that nitrogen is lost also as protein and amino acids in the dialysate, and occasionally in appreciable quantities in the urine. It is of course possible to measure the *protein nitrogen losses* directly, and calculate the nitrogen loss from this using the fact that 0.16 of protein is nitrogen, and add this to the urea nitrogen losses. Routine estimates of *amino acid losses* in dialysate are not done, but an average figure is 0.5 g N/24 h, equivalent to 3.12 g protein/24 h. Other nitrogen losses, principally *faecal nitrogen losses* can be estimated to be:

$$\frac{0.031 \text{ IBW}}{0.16} \text{ g protein/24 h}$$

IBW = ideal body weight (kg) for height, from National Health and Nutrition Evaluation Survey (NHANES) tables (see below).

Normalisation of data

A normalised PCR or PNA (protein equivalent of the total nitrogen clearance) can be calculated to compare an individual patient's value with published standards or data, but there is debate about the method of normalisation. One could use actual body weight, dry body weight or oedema-free body weight, or ideal body weight from NHANES tables [Frisancho 1984]. *We advocate* that the ideal body weight from NHANES tables be utilised, since one is aiming to achieve nutritional intake based on ideal weights rather than actual weights.

A number of computer based programmes incorporating many of the features discussed above are available, some from commercial sources. Using these it is easy to calculate values of *Kt/V*, creatinine clearance and PCR (PNA) but it is important to be aware of what the normalisation factors are, as well as of how GFR is calculated and what measures are included in the data input.

As in haemodialysis, in patients on CAPD there is a statistically significant relationship between *Kt/V* and PCR; however, the clinical and mathematical significance of this correlation remains controversial [Lindsay and Spanner 1989; Blake *et al* 1991; Lindsay *et al* 1992; Harty *et al* 1994].

Other forms of peritoneal dialysis

All the discussion in the preceding paragraphs applies only to 'standard' CAPD. The equivalence of these data to those obtained using newer forms of machine assisted dialysis with 'dry' periods or nocturnal machine dialysis is not yet clear, and there are as yet no established methods for setting or assessing targets for dialysis in these circumstances.

[The advice given by Dr J E Tattersall and Dr N A Hoenich on urea kinetic modelling is acknowledged with thanks.]

Glomerular filtration rate in patients on dialysis

A4.5 Renal tubular secretion of creatinine accounts for a substantial fraction of renal creatinine clearance, and this proportion increases with renal failure; thus a more accurate estimate of GFR should be used than creatinine clearance alone. This is simply achieved by averaging the value of renal urea and renal creatinine clearances, or alternatively (and perhaps preferably) using the creatinine clearance following 400 mg cimetidine bd beginning 12 hours before the start of the 24 h urine collection [van Olden *et al* 1996].

If available locally, single injection methods of measuring the very low GFR of the CAPD patient may be employed as an alternative. Iohexol [Swan *et al* 1996], inulin, ^{131}I-iothalamate or ^{51}Cr-edetate may be used, with extension of the blood sampling period to 24 hours; see Cameron and Greger [1998] for further details.

Histo-compatibility laboratory tests

A4.6 The following standard descriptions of histocompatibility laboratory tests are those of the British Society for Histocompatibility and Immunogenetics.

■ ***Serological phenotyping tests***

Name	Description and purpose
1. HLA-ABC phenotyping	1. Serological typing of HLA Class I (A, B and C) specificities using the complement dependent cytotoxicity (CDC) assay for the purpose of HLA typing in transplantation, disease association and platelet transfusion.
2. HLA-DR & DQ phenotyping	2. Serological typing of HLA Class II (DR and DQ) specificities by methods and for purposes as in (1).
3. HLA-ABC DR & DQ genotyping	3. By methods as in (1) and (2), performed on family members for the purpose of determining segregation and identity of HLA haplotypes, for use in HLA matching for living related transplantation of solid organs or marrow.
4. Lymphocyte crossmatch	4. Complement dependent cytotoxicity crossmatch (CDCXM) to detect donor-specific cytotoxic antibodies in recipient sera using donor lymphocytes.
5. T-lymphocyte crossmatch	5. As in (4) but using purified donor T-lymphocytes.
6. B-lymphocyte crossmatch	6. As in (4) but using purified donor B-lymphocytes.
7. Autologous lymphocyte, or T or B lymphocyte crossmatch	7. CDCXM using recipients own lymphocytes, or separated T or B lymphocytes and sera, to detect autoreactive lymphocyte-specific antibodies.
8. DTT crossmatch	8. CDCXM using DTT (dithiothreitol) treated sera or cells to determine the IgG or IgM class of the antibody.
9. AHG crossmatch	9. AHG (anti-human globulin) augmented CDCXM to detect low levels of specific antibodies in sera.

Name	Description and purpose
10. Flow cytometry crossmatch (FCXM)	10. Crossmatch using donor lymphocytes, and recipient sera treated with a fluorochrome labelled second antibody, in order to detect complement and non-complement fixing donor-specific antibodies.
11. Serum screening for HLA Class I antibodies: using selected cell panel	11. CDC assay to determine the presence of specific HLA-A, -B and -Cw antibodies using an HLA-typed reference cell panel representing known specificities and incorporating uncommon allelic associations.
12. Serum screening for HLA Class II antibodies: using selected cell panel	12. As (11) but using a cell panel of B-lymphocytes or CLL (chronic lymphocytic leukaemia) cells representing known HLA-DR, -DQ specificities.
13. Serum screening for HLA Class I and/or Class II antibodies: using random cell panel	13. CDC assay to determine the presence of HLA-A, -B and -Cw and/or HLA-DR, -DQ antibodies using a randomly selected panel of cells.
14. DTT serum screening for HLA Class I and/or Class II antibodies	14. CDC assay to determine IgG or IgM class of antibody using DTT treated recipient sera and random or selected cell panel.

DNA-based phenotyping tests

Name	Method codes*	Description and purpose
15. HLA Class I DNA typing: low resolution	B, C, G	15. Determination of HLA-A, -B, -Cw allelic specificity by DNA analysis with a range of DNA probes or PCR primers giving definition comparable to serological typing.
16. HLA Class I DNA typing: high resolution	B, C, F, G	16. Determination of HLA-A, -B, -Cw allelic specificity by DNA analysis with a range of DNA probes, PCR primers or sequence-based methods giving high resolution definition.
17. HLA Class II DNA typing: low resolution	A, B, C, D, G	17. Determination of HLA-DR, -DQ and -DP allelic specificity as in (16).
18. HLA Class II DNA typing: high resolution	B, C, F, G	18. Determination of HLA-DR, -DQ and -DP allelic specificity as in (17).
19. HLA Class I and Class II matching by conformational analyses	E, H, J	19. Determination of allelic match or mismatch for HLA between recipient and donor.

* These method codes A to J are explained in the table below

Biochemical typing methods

Name	Description and purpose
20. HLA Class I biochemistry	20. Phenotyping of expressed HLA-A, -B, -Cw antigens by radiolabelling of proteins followed by immune precipitation and 1- or 2-dimensional isoelectric focusing. Used for fine analysis of HLA Class I specificities

DNA tests and their standard acronyms/abbreviations

Code	Recommended acronym or abbreviation	Full name of test	Synonyms
A	RFLP	Restriction fragment length polymorphism analysis.	Southern blot
B	PCR-SSOP	Polymerase chain reaction - sequence-specific oligonucleotide probe typing. Two formats are used: dot-blot and reverse dot-blot. 'Oligocapture' uses microtitre tray-based formats.	PCR-SSO PCR-ASO PCR-Oligocapture
C	PCR-SSP	Polymerase chain reaction - sequence-specific primers	PCR-ARMS
D	PCR-RFLP	Polymerase chain reaction - restriction fragment length polymorphism	PCR-AFLP
E	PCR-SSCP	Polymerase chain reaction - single-stranded conformational polymorphism	
F	PCR-SBT	Polymerase chain reaction - sequence-based typing	Direct sequencing
G	PCR-HPA	Polymerase chain reaction - hybridisation protection assay	
H	PCR-heteroduplex analysis	Polymerase chain reaction - heteroduplex analysis	PCR-fingerprinting
J	PCR-UHG crossmatching	Polymerase chain reaction - heteroduplex analysis with a universal heteroduplex generator	

Patients with other illnesses or disabilities: comorbidity

Survival and measurement of outcome

A4.7 Survival remains the ultimate measure of the success of renal replacement therapy for end stage renal failure (ESRF), a universally fatal condition. It is used therefore as a measure of quality to compare performance, both within and between centres providing such treatment. However, the cost and outcomes of providing the service are influenced by the age and general health of patients accepted for treatment (see 4.10), so any comparative audit or setting of standards in dialysis or transplantation must take account of factors present in the patients, other than the renal failure itself.

It is important also to include survival and other information on very frail or very ill patients who die within a few weeks of beginning dialysis treatment (see Chapters 5 and 6). This has not been universal practice either in the UK or internationally. For example, European data from the ERA Registry include such patients, whereas the US Renal Data System excludes all those who do not survive to 90 days from beginning dialysis. However, the ERA Registry, although it has analysed the effects of age in some detail [Valderrábano *et al* 1995], has not taken comorbid conditions into account other than diabetes mellitus and systemic disease involving the kidney (eg lupus).

Increasing age and comorbidity in ESRF

The importance of these considerations continues to increase as older patients and those with other comorbid illnesses or disabilities are accepted for treatment for their ESRF. For example, the median (average) age of those accepted for dialysis in the UK rose from 47 years in 1977 to 60 years in 1992 [Department of Health 1996a; Roderick 1997]. This population includes, inevitably, a higher proportion of socially deprived, frail patients with decreased mobility and more mental disability. Comparison of global survival data between centres or regions will be meaningless unless the influences of comorbidity and age are considered.

Comorbid conditions that influence survival

Survival of patients during treatment for ESRF, and general indices of mobility and well-being, have been shown to be influenced by age and by many comorbid conditions such as diabetes mellitus, ischaemic heart disease, congestive heart failure, liver disease, respiratory disease and peripheral vascular disease. The publications have emanated mostly from the United States [McClellan *et al* 1991, 1992; Wright 1991; US Renal Data System 1992; Collins *et al* 1994] but also from the UK [Khan *et al* 1993, 1996] and other countries [Nicolucci *et al* 1992]. If the severity of each condition is taken into account as well, then the complexity of the problem is evident.

Assessment of comorbidity

The Index of Coexisting Disease (ICED) has been use in a number of other medical conditions, particularly cancers [Charleson *et al* 1987; Bennett *et al* 1991], as well as hip replacement [Greenfield *et al* 1993], to determine its effect upon outcome. This involves calculating a weighted index of comorbidity taking into account several levels of severity; so far it has been little applied to renal disease [Nicolucci *et al* 1992; Athienites *et al* 1994].

The first edition of this standards document [Renal Association 1995] quoted the review of renal services in England completed in 1994 [Department of Health 1996a] which identified a very simplified classification of relative risk for patients undergoing treatment for ESRF, which (slightly modified) is:

Standard risk:	non-diabetics under the age of 55
Medium risk:	non-diabetics aged 55–64 and diabetics aged 15–54
High risk:	non-diabetics 65 and older, diabetics 55 and older, and all HIV positive patients

This simple approach still seems applicable in making comparisons, and *the targets throughout this present document have been set only for standard risk patients*, ie non-diabetic, HIV negative, <55 years old. However, this evaluation ignores other comorbidity and has not yet been tested prospectively. It can be regarded only as an interim suggestion until individual comorbidities can be allocated specific weightings in calculating overall risk. The UK Renal Registry intends to collect comorbidity data, both at entry and annually thereafter, to refine this simple approach; these data are shown below.

Recommendation

Data should be collected separately for standard, medium and high risk patients under treatment for ESRF as suggested above.

The presence or absence of the comorbid conditions listed below should be noted for all patients receiving ESRF, and the assessment repeated at least annually.

Comorbid conditions and their definition

The data upon which the following definitions are based are included in the data set being collected for the UK Renal Registry.

Diabetes mellitus	Hyperglycaemia requiring treatment OR Diabetic microvasculopathy
Peripheral vascular disease	Missing peripheral pulse(s) OR Claudication OR Ischaemic ulcers OR Revascularisation OR Amputation
Ischaemic heart disease	Known myocardial infarction OR Revascularisation/angioplasty OR Documented angina
Heart failure	Clinical signs of congestive heart failure OR Ejection fraction <40% on echocardiography

Cerebral vascular disease	Documented cerebrovascular accident OR Transient ischaemic attacks
Liver disease	Persistent enzyme evidence of hepatic dysfunction OR Biopsy evidence OR HBeAg or hepatitis C antigen (polymerase chain reaction) positive serology
Chronic obstructive airways disease (COAD)/ Respiratory failure	Diagnosis of exclusion in a patient with chronic bronchiolar obstruction and hyperinflated lungs
Malignancy	Presence of any malignant condition, other than basal cell carcinoma of the skin
HIV positive	Positive with any recognised serological test for HIV
Other	Inherited or congenital disorders with an impact on survival, eg oxalosis, cystic fibrosis, Down's syndrome, congenital heart disease

The position of smoking *per se* as a risk factor for patients with renal failure is still not clear. It will be expressed by the presence of COAD and vascular disease but for the moment it is being recorded as a separate item of data in the Renal Registry set.

We hope that the collation of these data by the UK Renal Registry will provide more accurate assessment of comorbidity than the current method which takes account only of age and diabetes.

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The literature has been reviewed up to August 1996, and selectively from September 1996 to early 1997. **CT** = prospective controlled trial. **Review** = literature review including meta-analyses.

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