

Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews

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Health Technology Assessment
NHS R&D HTA Programme



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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Acute Sector Panel.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will, in England, be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature but the term has a constant meaning throughout this review.

Glossary

Acute renal failure The usually sudden and potentially reversible loss of renal function.

Allocative efficiency This type of efficiency is addressed by cost-benefit analysis. It is about achieving the optimal allocation of resources across all possible uses of such resources. Therefore, if an intervention is shown to be more effective and more costly than an alternative, a decision has to be taken as to whether the extra cost is justified in terms of improved effectiveness; that is, will the input of more resources to that particular area of care enhance allocative efficiency?

Automated cyler machine A device used to administer peritoneal dialysis for a defined period usually at night time. The patient usually needs to make only one connection and the automated cyler machine carries out the prescribed dialysis exchanges. A variety of automated cyler machines are available.

Automated peritoneal dialysis* There are a number of new technologies which are adaptations of continuous ambulatory peritoneal dialysis and which have the potential to improve quality of life for some patients. These include intermittent peritoneal dialysis, continuous cyclic peritoneal dialysis and night-time intermittent peritoneal dialysis. These new technologies require more expensive dialysis fluids or dialysis machines or both.

Blinding (synonym: masking)* Keeping secret group assignment (e.g. to treatment or control) from the study participants or investigators. Blinding is used to protect against the possibility that knowledge of assignment may affect patient response to treatment, provider behaviours (performance bias) or outcome assessment (detection bias). Blinding is not

always practical (e.g. when comparing surgery to drug treatment).

The importance of blinding depends on how objective the outcome measure is; blinding is more important for less objective outcome measures such as pain or quality of life.

Chronic renal failure* Kidneys slowly destroyed over months or years. To begin with there is little to see or find, which means that many patients present for medical help very late in their disease, or even in the terminal stages.

Cochrane Collaboration* An international organisation that aims to help people make well-informed decisions about health by preparing, maintaining and ensuring the accessibility of systematic reviews of the benefits and risks of healthcare interventions.

Cochrane Library* A collection of databases, published on disk and CD-ROM and updated quarterly, containing the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, the Database of Abstracts of Reviews of Effectiveness, the Cochrane Review Methodology Database and information about the Cochrane Collaboration.

Cochrane review* A Cochrane review is a systematic, up-to-date summary of reliable evidence of healthcare benefits and risks. Cochrane reviews are intended to help people make practical decisions. For a review to be called a 'Cochrane review', it must be in the parent database maintained by the Cochrane Collaboration. This composed of modules of reviews submitted by Collaborative Review Groups (CRGs) registered with the Cochrane Collaboration. The reviews contributed to one of the modules making up the parent database

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are refereed by the editorial team of the CRG, as described in the CRG module. Reviewers adhere to guidelines published in the *Cochrane Handbook*. The specific methods used in a review are described in the text of the review. Cochrane reviews are prepared using Review Manager software provided by the Collaboration and adhere to a structured format that is described in the Handbook.

Concealment of allocation* The process used to prevent foreknowledge of group assignment in an RCT, which should be seen as distinct from blinding. The allocation process should be impervious to any influence by the individual making the allocation by having the randomisation process administered by someone who is not responsible for recruiting participants: for example, a hospital pharmacy or a central office.

Methods of assignment such as date of birth and case record numbers (see quasi-random allocation) are open to manipulation. Adequate methods of allocation concealment include: centralised randomisation schemes; randomisation schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes.

Confidence interval* The range within which the 'true' value (e.g. size of effect of an intervention) is expected to lie with a given degree of certainty (e.g. 95% or 99%). Note: Confidence intervals represent the probability of random errors but not systematic errors (bias).

Continuous ambulatory peritoneal dialysis*

In this technique, dialysis fluid is introduced into and withdrawn from the peritoneal cavity (which is around the bowel) via a silastic tube (catheter). Waste products are removed from the blood across the peritoneal membrane. 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. Dialysis fluid is withdrawn from the peritoneal cavity after a dwell of 4–5 hours during the day and about 8 hours overnight and fresh fluid introduced. This

procedure, which takes about 20 minutes, is called an exchange and occurs four times daily.

Continuous cyclic peritoneal dialysis This is a form of peritoneal dialysis in which all connections and preparation of equipment usually takes place at bedtime in the privacy of the home. To administer it a peritoneal cyclor is required and the process is usually carried out at night when the patient is asleep. It is called continuous because fluid is usually left in the abdomen during the day. If no dialysis fluid is left in the abdomen during the day, it is called nocturnal intermittent peritoneal dialysis.

Continuous data* Data with a potentially infinite number of possible values along a continuum. Height, weight and blood pressure are examples of continuous variables.

Cost-effectiveness analysis* An economic analysis used to compare effectiveness and cost of health interventions in which either:

- effects of the interventions are known to be equal and so the option to be recommended is that which is least (or less) costly (some times known as 'cost-minimisation analysis'); or
- effects and costs differ across interventions; hence, the option to be recommended is that with the lowest (or lower) ratio of cost per unit of health gain, as implementation of this option will lead to the most (or more) effective use of a fixed budget.

Creatinine* A natural waste product of muscle metabolism which is normally excreted by the kidney. When renal function is reduced the level of creatinine in the blood rises and the amount cleared from the kidneys (creatinine clearance) falls. These measures are used as a broad approximation of the prevailing level of renal function.

Crossover trial* A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the

effects of the first treatment may carry over into the period when the second is given.

Data abstraction The systematic procedure of transcribing data from included studies. Data abstracted typically include a description of the intervention, population and setting together with outcomes data.

Decision analysis* A technique used to aid decision-making under conditions of uncertainty by systematically representing and examining all of the relevant information for a decision and the uncertainty around that information. The available choices are plotted on a decision tree. At each branch, or decision node, the probabilities of each outcome that can be predicted are estimated. The relative worth or preferences of decision-makers for the various possible outcomes for a decision can also be estimated and incorporated in a decision analysis.

Dichotomous data (synonym: binary data)* Observations with two possible categories, such as dead/alive, smoker/non-smoker, present/non-present.

End-stage renal disease End-stage renal disease is defined as the last stage in the course of renal failure which cannot be controlled by conservative management and when the patient requires either dialysis or a kidney transplant in order to maintain life.

Exchange Used in continuous ambulatory peritoneal dialysis, this term refers to the process of draining fluid out of the peritoneal cavity and instilling a fresh bag of dialysate into the peritoneal cavity.

Exit site That site on the skin surface where the peritoneal dialysis catheter exits.

Fixed-effect model* A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed-effect model. Variation between the estimates of effect from each study (heterogeneity) does not affect the confidence interval in a fixed-effect model.

Grey literature Refers to literature that is not widely published such as dissertations, theses and government reports.

Haemodialysis 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. The patient's circulation is attached to a machine through which fluid is passed and exchange can take place.

Heterogeneity* In systematic reviews heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between 'statistical heterogeneity' (differences in the reported effects), 'methodological heterogeneity' (differences in study design) and 'clinical heterogeneity' (differences between studies in key characteristics of the participants interventions or outcome measures).

Statistical tests of heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance. However, these tests have low statistical power (see also homogeneity).

Homogeneity* In systematic reviews homogeneity refers to the degree to which the results of studies included in a review are similar. 'Clinical homogeneity' means that, in trials included in a review, the participants interventions and outcome measures are similar or comparable. Studies are considered 'statistically homogeneous' if their results vary no more than might be expected by the play of chance (see also heterogeneity).

Hyperkalaemia An abnormally high level of potassium in the blood usually defined as greater than 5.0 mmol/l (the ranges may vary from laboratory to laboratory).

Intention-to-treat* An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether

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they received it or not. Intention-to-treat analyses are favoured in assessments of effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.

Intermittent peritoneal dialysis* An older but still useful technique of peritoneal dialysis in which fluid is instilled into the peritoneal cavity at regular intervals but for a limited period. The process may be repeated.

Kt/V Measure of dialysis adequacy.

Markov model A Markov process is a technique used in decision analysis (see Decision analysis). In a standard decision tree analysis a patient moves through states, for example, from not treated to treated to final outcome; however, in a Markov process a patient would move between states, for example, backwards and forwards between continuous ambulatory peritoneal dialysis and haemodialysis. There are some states, however, that once entered cannot be left. These are defined as 'absorbing states' (in models of medical interventions such states are normally defined as death).

Membranes* The material used as a filtering agent in dialysers. Many are formed from a cellulose base, others from synthetic materials constructed in an attempt to adjust the molecular weight of the substances filtered and to reduce any reaction in the patient which may result from the contact of blood with the membrane surface.

MeSH (medical subject headings)* A standard set of keyboarding terms used by the US National Library of Medicine to index articles in *Index Medicus* and Medline. Designed to reduce problems that arise from, for example, differences in British and American spelling, the MeSH system has a tree structure in which broad subject terms branch into a series of progressively narrower subject terms.

Meta-analysis* The use of statistical techniques in a systematic review to integrate the results of the included studies. Also used to refer to systematic reviews that use meta-analysis.

Methodological quality* (synonyms: validity, internal validity) The extent to which the design and conduct of a trial are likely to have prevented systematic errors (bias). Variation in quality can explain variation on the results of trials included in a systematic review. More rigorously designed (better 'quality') trials are more likely to yield results that are closer to the 'truth'.

Odds ratio* The ratio of the odds of an event in the experimental (intervention) group to the odds of an event in the control group. Odds are the ratio of the number of people in a group with an event to the number without an event. Thus, if a group of 100 people had an event rate of 0.20, the event happened to 20 people and did not happen to 80, and the odds would be 20/80 or 0.25.

An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an odds ratio of less than one indicates that the intervention was effective in reducing the risk of that outcome. When the event rate is small, odds ratios are very similar to relative risks.

Peritoneal catheter This is a length of straight or curled silicon rubber or polyurethane tubing with numerous side holes at the distal end. Usually one or two Dacron® cuffs are present on the catheter to provoke a local inflammatory response to anchor the catheter firmly into a subcutaneous tunnel. The catheter itself is placed in the peritoneal catheter by a surgeon or a nephrologist.

Peritoneal dialysis A modality of renal replacement therapy in which dialysis is carried out by instilling fluid into the potential peritoneal cavity through a catheter. The fluid is then allowed to remain in the peritoneal cavity for a time and dialysis occurs by diffusion and by ultrafiltration. The fluid is then drained out and fresh dialysate is instilled into the peritoneal cavity to continue the process.

Peritoneal membrane A mesothelial membrane which lines the inner wall of the abdominal cavity (perietal peritoneum) and also covers the abdominal viscera (visceral peritoneum). The membrane is actually a heterogeneous series of tissue barriers

between blood and the peritoneal space which normally contains no free fluid. It can be used for purposes of dialysis as described above under peritoneal dialysis.

Permuted index Allows exploration in Medline of every MeSH term which contains a particular word, for example, all MeSH terms containing the word 'dialysis' such as peritoneal dialysis.

Peto's method* A way of combining odds ratios that has become widely used in meta-analysis. The calculations are straightforward and understandable but the method produces biased results in some circumstances. It is a fixed-effect model.

Protein catabolic rate The rate at which protein is catabolised by the body. In patients who are in a steady state, protein catabolic rate equals the dietary intake of protein.

Protocol* The plan or set of steps to be followed in a study. A protocol for a systematic review should describe the rationale for the review, the objectives and the methods that will be used to locate, select and critically appraise studies, and to collect and analyse data from the included studies.

Pruritus Skin itch.

Quality assessment The extent to which the design and conduct of a trial are likely to have prevented systematic errors (bias). Variation in quality can explain variation in the results of trials included in a systematic review. More rigorously designed (better 'quality') trials are more likely to yield results that are closer to the 'truth'.

Quasi-random allocation* A method of allocating participants to different forms of care that is not truly random, for example, allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study (e.g. alternation).

Quasi-randomised trials* A trial using a quasi-random method of allocating participants to different forms of care. There is a greater risk of selection bias in quasi-random trials in

which allocation is not adequately concealed compared with randomised controlled trials with adequate allocation concealment.

Random allocation* A method that uses the play of chance to assign participants to comparison groups in a trial, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual or unit being entered into a trial has the same chance of receiving each of the possible interventions. It also implies that the probability that an individual will receive a particular intervention is independent of the probability that any other individual will receive the same intervention.

Random effects* A statistical model sometimes used in meta-analysis, in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (or confidence interval) of the results of a meta-analysis (see Fixed-effect model). If there is significant heterogeneity among the results of the included studies, random-effects models will give wider confidence intervals than fixed-effect models.

Randomisation* Method used to generate a random allocation sequence, such as using tables of random numbers or computer-generated random sequences. The method of randomisation should be distinguished from concealment of allocation because of the risk of selection bias, despite the use of randomisation, if there is not adequate allocation concealment.

For instance, a list of random numbers may be used to randomise participants but, if the list is open to the individuals responsible for recruiting and allocating participants, those individuals can influence the allocation process, either knowingly or unknowingly.

Randomised controlled trial (synonym: randomised clinical trial)* An experiment in which investigators randomly allocate eligible people into groups (e.g. treatment and control) to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.

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Reference Manager* A software package designed to manage bibliographic references. Sometimes confusingly referred to as RefMan (see RevMan). Examples of other similar packages are Papyrus and ProCite.

Review Manager* Software developed for the Cochrane Collaboration to assist reviewers in preparing Cochrane reviews. Reviewers enter their protocols and reviews into RevMan, from which they can be imported into ModMan by a Collaborative Review Group coordinator for inclusion in the parent database and the Cochrane Database of Systematic Reviews as part of the Group's edited module.

Review protocol see Protocol.

Search strategy*

(1) The methods used by a Collaborative Review Group registered with the Cochrane Collaboration to identify trials within the Group's scope. This includes handsearching relevant journals, searching electronic databases, contacting drug companies, other forms of personal contact and checking reference lists. Groups must describe their search strategy in detail in their module. Reviewers can refer to the Group's search strategy when preparing a Cochrane Review and, if necessary, supplement this with a description of their own additional searches.

(2) The methods used by a reviewer to locate relevant studies, including the use of a Collaborative Review Group's trials register.

(3) The combination of terms used to identify studies on an electronic database such as Medline.

Serum urea Urea has a molecular weight of 67 and is a product of metabolism of amino acid. The normal serum concentration of urea is 4–6.6 mmol/l. A high serum urea concentration is seen in patients with renal failure but may also be seen in patients with gastrointestinal haemorrhage and dehydration.

Systematic review (Synonym: systematic overview)* A review of a clearly formulated question that uses systematic and explicit

methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies (see also Cochrane review).

Technical efficiency Whereas an allocative efficiency perspective addresses the question of whether to carry out or expand an activity, technical efficiency addresses the issue of how best to undertake an activity once a decision has been made to carry it out. Strictly, technical efficiency is ensuring the production of a given output with less of one input and no more of other inputs. Cost-effectiveness, which is about minimising the costs of a given output, implies technical efficiency.

Transfer sets In continuous ambulatory peritoneal dialysis, a solution container is connected to the patient's peritoneal dialysis catheter by a length of plastic tubing called a transfer set. There are two types of transfer sets, each requiring a different method of performing the exchange. These can be classified into straight transfer sets and the Y-transfer set.

Tunnel infections Those which occur in the tunnel portion of catheters. In peritoneal dialysis catheters, tunnel infections usually require removal and replacement of catheter.

Weighted mean difference (in meta-analysis)* A method of meta-analysis used to combine measures on continuous scales (such as height), where the mean, standard deviation and sample size in each group are known. The weight given to each study (e.g. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and, in the statistical software in RevMan and the Cochrane Database of Systematic Reviews, is equal to the inverse of the variance. This method assumes that all of the trials have measure the outcome on the same scale.

* Reproduced with permission from The Cochrane Collaboration Handbook, v. 3.0, December 1996, and the Renal Purchasing Guidelines, NHS Executive, May 1996.

List of abbreviations

ACE	angiotensin converting enzyme	OR	odds ratio
BCM	biocompatible*	PCR	protein catabolic rate
BICM	bio-incompatible*	PKD	polycystic kidney disease
BPH	benign prostatic hyperplasia	PMMA	polymethylmethacrylate
BUN	blood urea nitrogen*	RCT	randomised controlled (clinical) trial
CAPD	continuous ambulatory peritoneal dialysis	RRT	renal replacement therapy
CCPD	continuous cyclic peritoneal dialysis	SD	standard deviation*
CCT	controlled clinical trial	SEM	standard error of the mean
CI	confidence interval	UFc	ultrafiltration coefficient
EPO	erythropoietin	URR	urea reduction ratio
ESRD	end-stage renal disease	WMD	weighted mean difference
HDL	high-density lipoprotein		
LDL	low-density lipoprotein		
NNT	numbers-needed-to-treat		

* Used in figures and tables



Executive summary

Objectives

- To review systematically the literature on six major topics in dialysis therapy for patients with end-stage renal disease (ESRD).
- To link clinical effectiveness with cost (resource use) in an economic analysis to assess efficiency.
- To suggest implications for clinical practice and policy needs.
- To indicate areas for further research.

Methods

Cochrane Collaboration methods were adopted and are described in detail in the full report.

Results

About 16,000 abstracts were considered and about 2300 possible randomised controlled trials (RCTs) relevant to ESRD (excluding transplantation) identified; 537 were relevant to the six topics and only 47 actually met the eligibility criteria and were included in the review. A total of 820 papers were used for the economic evaluation.

1. Synthetic compared with cellulose-based membranes in haemodialysis treatment for ESRD

The inclusion criteria were met by 22 studies. The incidence of nausea and vomiting was significantly less with synthetic than with cellulose membranes. Predialysis β_2 microglobulin concentrations were significantly lower with high-flux synthetic membranes. In a 6-year study, the incidence of amyloid disease was less with high-flux synthetic membranes.

Plasma triglyceride was lower with synthetic high-flux membranes (one study) and serum albumin was higher. Whether the differences were attributable to the membrane material or to the flux is unclear. There was no other significant difference.

When compared with modified cellulose membranes, the incidence of pruritus was less with synthetic membranes. The additional benefits of synthetic membranes were achieved at additional cost.

2. Bicarbonate-buffered compared with acetate-buffered dialysate in haemodialysis treatment for ESRD

The inclusion criteria were met by 18 studies. There was a significant reduction with bicarbonate dialysis in the number of haemodialysis treatments complicated by headaches, nausea/vomiting, symptomatic hypotension and non-specific intolerance. There was no clear evidence of improved cardiovascular stability, lipid profile or biochemical indicators of renal bone disease. Economic evaluation showed the cost of the self-mix bicarbonate buffer to be similar to that of acetate.

3. Short-duration compared with standard-duration haemodialysis for ESRD

One study with 165 patients was identified. It compared ≤ 3.5 hours dialysis with > 3.5 hours dialysis three times a week. There was no significant difference in mortality. Hospitalisation rates were greater in the short-duration group. There was no conclusive difference in the incidence of intradialytic adverse symptoms between the groups. Blood pressure control was worse in the short-duration group. There was insufficient evidence to judge relative efficiency.

4. Continuous ambulatory peritoneal dialysis (CAPD) delivery systems: Y-set/modified Y-set versus standard spike as treatment for ESRD

Six studies met the inclusion criteria. The number of patients with at least one episode of peritonitis was significantly lower in patients using Y-set delivery systems. All but one study demonstrated a significant increase in the number of months per episode of peritonitis with the Y-set delivery systems. All studies showed a significant increase in the time to first episode of peritonitis with the Y-set system. There was no significant reduction in the number of patients who suffered exit-site infections or tunnel infections with the Y-set system. No study addressed technique failure. Benefits are achievable at extra cost.

5. Continuous cycler-assisted peritoneal dialysis (CCPD) compared with CAPD as treatment for ESRD

One study of 82 patients met the inclusion criteria. There were no significant differences in the num-

ber of patients with peritonitis, catheter exit-site infections or catheter tunnel infections. The mean number of peritonitis episodes per patient per year was significantly lower with CCPD. There was no significant difference in Kt/V, six-monthly serum creatinine, urea or phosphate. Fewer patients on CCPD needed to change dialysis technique but this was not statistically significant. Patient preference could not be adequately assessed because of the parallel group trial design. The estimated cost per episode of peritonitis avoided is considerable.

6. Haemodialysis compared with CAPD as treatment for ESRD

No relevant RCTs were identified. Because of the poor quality of the study designs used to obtain primary data for economic analyses, it is not possible to judge whether any assumed extra benefits provided by haemodialysis are worth any extra costs that may be incurred.

Conclusions

Implications for policy

- The moderate benefits of high-flux synthetic membranes are currently achieved at additional cost. For general use, cellulose (particularly modified cellulose) membranes are appropriate. Synthetic membranes may be appropriate for patients experiencing persistent nausea and vomiting and for patients likely to be treated by haemodialysis for many years. The price of high-flux synthetic membranes is likely to fall in the future and policy recommendations should be kept under review.
- Bicarbonate dialysis is preferable to acetate dialysis for the haemodialysis of patients with ESRD, producing fewer unwanted effects at a similar cost.
- There is no evidence that reduced dialysis duration (≤ 3.5 hours three times per week) decreases mortality and it may increase morbidity. If reduced dialysis duration regimens are implemented on the basis of patient preference or assumed lower cost, their unproven safety should be explicitly acknowledged.
- Y-set delivery systems significantly reduce the incidence of peritonitis. Given that recurrent peritonitis is a major cause of technique failure, the additional cost is likely to be justified.
- CCPD showed benefit in one patient outcome but is more expensive than CAPD. It is suggested that CCPD should only be offered as an alternative to CAPD, at present, to patients for whom there is a specific indication.
- Data are not available to allow reliable conclusions to be drawn about the relative

effectiveness and efficiency of haemodialysis and CAPD.

- Dialysis for ESRD intrudes greatly into people's daily lives. Informed patient preference, based on evidence of effectiveness and efficiency, should be taken into account when policy is decided.

Recommendations for research

- Further multicentre pragmatic RCTs with economic evaluations concentrating on primary outcomes of major importance to patients are required to compare the different dialysis membranes available. These should take into account membrane reuse, their properties, including flux and material, and should include modified cellulose and low-flux synthetic membranes which may be less expensive than their high-flux counterparts. The trials should include older patients and those with comorbid illnesses.
- A large multicentre pragmatic RCT comparing haemodialysis treatment duration policies is required. Such a trial should include the longer duration haemodialysis practised in other parts of Europe, have minimum exclusion criteria, a long follow-up period and minimum data collection, concentrating primarily on patient morbidity and mortality.
- More evidence of the effect on patient outcomes and costs of technique failure would further inform the decision about the use of Y-set systems.
- Further RCTs with economic evaluations are required comparing CCPD with CAPD, with particular reference to peritonitis, technique failure rates and patient preference. Studies are also required to compare CCPD with haemodialysis to determine whether it is efficient to provide CCPD for those patients who have a relative contraindication to CAPD and who would otherwise be treated by haemodialysis.
- The issue facing the health services is not whether to have CAPD or haemodialysis but rather the balance of provision between the two modalities. International variations in usage show that a large proportion of patients requiring dialysis for ESRD could be managed initially with either CAPD or haemodialysis. Information is required about the relative costs, benefits and risks of policies of starting with one or other modality. Information on benefits, risks and costs should come from a pragmatic RCT of policies based on starting with CAPD or haemodialysis.
- Further systematic reviews are required in other aspects of dialysis where there are practice options.
- The results of the on-going large American study (HEMO) should be taken into account when the research agenda is decided.

Chapter I

Introduction

The authors were commissioned under the NHS Executive Research and Development Programme to undertake a systematic literature review of the effectiveness of dialysis therapy for end-stage renal disease (ESRD). There are many points in the management of patients on dialysis where choices require to be made. Using a dialysis decision tree, six of them were selected in which there were known variations in practice and in which there were likely to be significant resource implications. Six reviews were undertaken by a multidisciplinary team of clinicians, health services researchers experienced in carrying out literature reviews and health economists using the standardised format of the Cochrane Collaboration. There is currently no agreed arrangement for incorporating economic analyses into Cochrane reviews; however, these have been added to each review and their findings included in the overall conclusions and summaries. A summary of the results of all reviews is given in chapter 4 and the full reviews, including the economic analyses, are included as appendices 4–9.

Background

When people with irreversible loss of kidney function reach that point in the course of their illness when their kidneys fail to support life, they are said to have ESRD. The only way in which they can then be kept alive is by renal replacement therapy (RRT). There are two types of RRT, dialysis and transplantation. Those needing RRT are likely to move between the various modalities of treatment; for example, they may begin with haemodialysis, move to continuous ambulatory peritoneal dialysis (CAPD), receive a renal transplant, and then return to haemodialysis if transplantation fails.

Although transplantation is the treatment of choice, the number of donor kidneys is limited and hence many patients require long-term or even life-long dialysis. Such therapy is not only associated with considerable morbidity and a significantly impaired quality of life but also imposes a major economic burden on the health service. In recent years, the number of patients accepted for dialysis in the UK has increased. In the UK in 1982, an average of 20 patients per

million of the population started dialysis.¹ This figure is now about 80 patients per million and will almost certainly rise further, particularly in areas where ethnic minorities comprise a high proportion of the population.^{2–4} As the number of patients receiving RRT increases, there is increased pressure to spend more on renal services and this is, quite rightly, raising concerns about the effectiveness and efficiency of current provision.

Methods of dialysis

Dialysis removes fluid, electrolytes and toxins that the failed kidney cannot excrete. It also allows buffering of the blood with alkali as the kidney can no longer correct the body's tendency to acidity. A fuller explanation is given in appendix 1. There are two principal modes of dialysis for patients with ESRD – haemodialysis and CAPD.

Haemodialysis

The artificial kidney (dialyser) used in haemodialysis contains a semi-permeable membrane; dialysis relies on the fact that small molecules such as urea and creatinine, which are usually excreted by the kidney, can pass across this membrane down a concentration gradient. Removal of fluid from blood is achieved by applying hydrostatic pressure across the membrane and acidosis is corrected by acetate or bicarbonate in the dialysis fluid (dialysate) that flows on the other side of the membrane. This procedure requires permanent easy access to the patient's circulation which is usually obtained by creating an arteriovenous fistula in the arm. Several types of dialysers, dialysates and 'dialysis machines' which monitor the procedure are commercially available, and the frequency and duration of dialysis sessions, dialyser membranes, dialysate composition and dialysis schedules vary from centre to centre. Haemodialysis can be carried out in the patient's home or in a satellite unit run by nursing staff, as well as in a large hospital dialysis unit.

CAPD and CCPD

The human peritoneal membrane is semi-permeable and, hence, can be used as a dialysis membrane. In CAPD, using the peritoneal membrane in this way requires a permanent catheter to be inserted in the abdomen through which the dialysing fluid (dialysate) is passed into the

peritoneal cavity. The small molecules normally excreted by the kidney, such as urea and creatinine, pass across the peritoneal membrane down a concentration gradient. Removal of fluid relies on an osmotic gradient across the membrane and this is created by using varying concentrations of glucose or carbohydrate polymer (Icodextrin) in the dialysis fluid. The dialysate is left in the peritoneal cavity for 6–8 hours to allow equilibration and then drained out and replaced with fresh fluid. Thus, peritoneal dialysis does not require a machine and can be carried out by patients in their own homes. Several types of catheter and dialysis fluid are available commercially and a range of management regimens have been advocated. Continuous cyclic peritoneal dialysis (CCPD) is a modification of CAPD in which the exchanges are performed overnight by a machine. Recently it has been proposed as an alternative to CAPD.

Variation in dialysis practice

Despite the marked differences between haemodialysis and CAPD there are surprisingly wide inter- and intra-national variations in the use of the two approaches. In part, this seems to reflect differing perceptions of the role of CAPD as an alternative to haemodialysis. In the 1980s, the criteria for accepting patients for dialysis in the UK were broadened, and older patients and those with co-morbid illnesses, such as heart disease and diabetes, were accepted for treatment. This coincided with the introduction of CAPD. In the UK, CAPD was seen as a way of allowing the treatment of an increasing number of patients without the need to create more haemodialysis facilities, purchase expensive machines and employ large numbers of highly trained staff. Currently in the UK, about 50% of new patients beginning dialysis are treated by CAPD; this contrasts with other countries, such as France, Germany, Italy and the USA, where CAPD is used in less than 20% of patients.

In certain patients it may not be possible to offer both types of dialysis therapy; those who have had extensive abdominal surgery, for example, may only be suitable for haemodialysis and those in whom the creation of vascular access has become impossible may be restricted to CAPD. Such medical issues, however, apply to a relatively small number of patients and, in the majority of cases, the choice of dialysis modality made by health personnel and/or the patient is based on non-medical factors.⁵

Outside the UK, the strongest determinant may be the higher levels of reimbursement associated with haemodialysis enjoyed by both the physician and dialysis facility.⁶ In the UK, factors which may

influence the choice include the distance of a patient's home from the renal unit and the presence of co-morbid illnesses.

Once these factors have been taken into account, it is generally considered by nephrologists in the UK that informed patient choice should be the major factor in influencing the selection of treatment modality, although, in fact, the decision is often influenced by the current availability of local facilities. Furthermore, the wide variation in dialysis practice is not limited to the choice between haemodialysis and CAPD. Once the decision to use haemodialysis has been made, selection of membranes, dialysis fluids and treatment protocols also vary, as do the choice of catheters, fluids and schedules for CAPD.

These variations may hide important differences within the range of approaches used for dialysis. All approaches to dialysis are associated with considerable morbidity and impose major restrictions on the lifestyles of those being treated. Dietary and fluid restrictions, dependence on dialysis technology for survival, and limits on ability to work and to travel, cause major stresses affecting the quality of life of both patients and their families, and it is important to assess, in as unbiased a way as possible, how such effects vary across dialysis approaches.

Costs of dialysis therapy

Dialysis therapy already consumes considerable health service resources and, as indicated above, as the number of patients likely to be treated each year increases, the stock of patients will rise, resulting in increasing pressure to spend more on renal services. The number of people on RRT (dialysis and transplantation) will increase until there is equilibrium between the numbers being accepted for treatment and the numbers dying. The number on dialysis will increase as a proportion of those treated if there is a shortage of kidney donors or if older people on RRT, especially those with co-morbid illnesses, are thought unsuitable for a renal transplant. Differences in costs between alternative approaches may therefore be very important. It has been estimated that when the rising number of dialysis patients reaches a plateau, 0.08% of the total number of patients will be consuming between 2% and 4% of the health budget.⁷ A recent review, however, highlighted the variation in estimated costs of dialysis in the UK. The authors of one of the reports cited estimated the annual cost per patient to be £18,000 for hospital haemodialysis and £13,000 for CAPD whereas, in another report, these costs were estimated to be £10,500 and £11,000, respectively.⁸ It was suggested in the review that some of these

cost variations may have occurred because of local differences in policies for administering and delivering dialysis services and differences in methodology used in assessing cost; for example, in some units the cost of CAPD fluids and expensive drugs such as erythropoietin (EPO) may be charged to general practitioners' budgets.

The systematic review

It was against this background of increasing pressure on resources and wide variations in practice that this systematic review of dialysis for ESRD was commissioned. We chose to address the issue in two complementary ways. Firstly, the aim was to review evidence of clinical effectiveness in terms of benefits and risks. Secondly, it was planned to link effectiveness with costs (resource use) in an economic analysis to assess efficiency. From the outset it was recognised that the choices were often not simply between one approach and another but rather between different policies, reflecting the fact that it may be good management in some circumstances to change from one technique to another. Thus, for example, the choice between haemodialysis and CAPD is a planning decision about which technique to use first, while recognising that it may be appropriate to switch to the alternative later.

The choice of questions addressed

To ensure that the review focused on the most important questions in dialysis, a 'dialysis decision tree' was developed (*Figure 1*).

Six points in the management of patients on dialysis were selected when major choices were

made, at which there were known to be variations in practice and for which there were likely to be significant resource implications (*Table 1*).

The topics for systematic reviews were chosen by two clinical nephrologists, based on recommendations from the NHS Executive, for two main reasons.

- There is wide variation in clinical practice in each of the six areas selected both in the UK and internationally.
- These areas all have important health economic implications.

In view of the resources available for this systematic review, both in terms of staffing and time, it was considered that only these six areas could be addressed in this project. There are, of course, many other areas in the management of ESRD by dialysis for which there are considerable resource implications and variations in practice. These topics could be considered for future systematic reviews.

Choice of literature to assess effectiveness and efficiency

The study concentrated on the evidence from randomised controlled trials (RCTs), even though it was suspected that there were likely to be relatively few such reports in the literature. Our concern was that observational studies, even well-conducted cohort studies, might be subject to selection biases of the same order of magnitude as the likely treatment differences.

It is now widely accepted that the only way to avoid such biases is by secure random allocation of the alternative approaches to care. The groups generated then only differ by chance in respect of

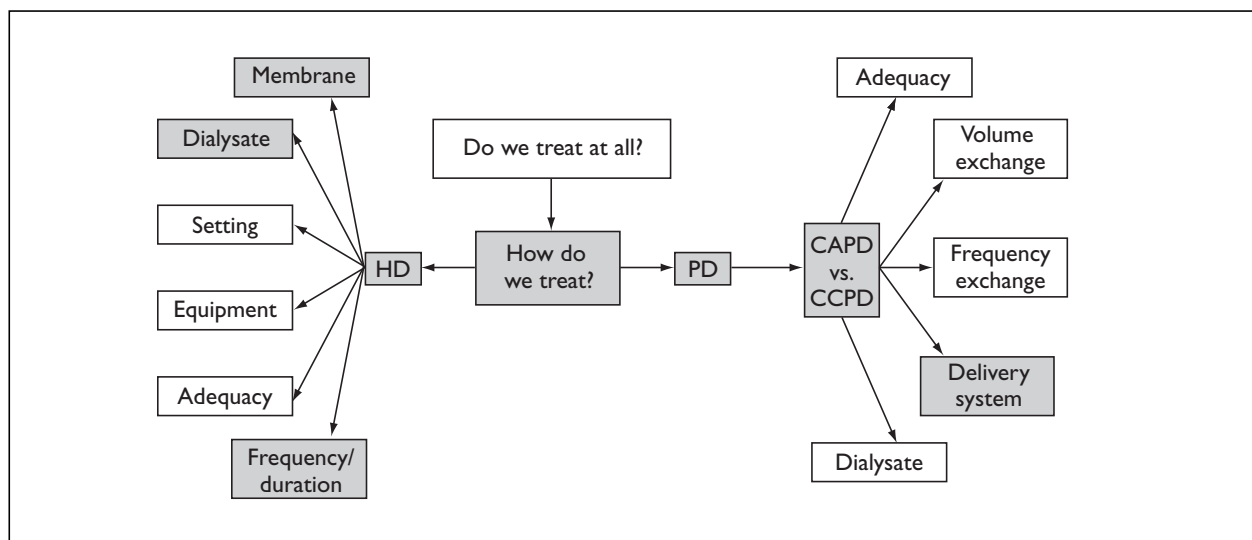


FIGURE 1 Dialysis decision tree (HD, haemodialysis; PD, peritoneal dialysis; □, topics selected for this series of reviews)

TABLE 1 Subjects addressed in the systematic reviews

1	Comparison of synthetic with cellulose-based membranes in haemodialysis treatment for patients with ESRD
2	Comparison of bicarbonate-buffered dialysate with acetate-buffered dialysate in haemodialysis treatment for patients with ESRD
3	Comparison of short-duration with standard duration dialysis treatments in haemodialysis treatment for patients with ESRD
4	Comparison of CAPD delivery systems – Y-set/modified Y-set versus standard spike in treatment for patients with ESRD
5	Comparison of CCPD with CAPD in treatment for patients with ESRD
6	Comparison of haemodialysis with CAPD as treatment for patients with ESRD

baseline prognostic variables. However, even when well-designed, the results of RCTs may still be of only limited value, because few are sufficiently large for precise enough estimates of treatment differences to be generated so that chance may be ruled out as an explanation. To overcome this, our plan was to consider the data from all similar trials in statistical meta-analysis, wherever possible.

Clearly, potential bias also needed to be minimised in the process by which data from comparable trials were brought together and synthesised. Systematic approaches to the identification of relevant studies and the abstraction of data from relevant reports were therefore used. These are discussed in detail later.

Although information on costs was sought in the reports of RCTs, the systematic literature search

for the economic analysis within each review was extended to identify previously conducted economic evaluations. The use of these data are described in detail later.

Choice of outcome measures

The main body of this report has been kept succinct by limiting it to a summary of activities and findings; individual topics are supported by appendices in which more detailed information is presented on the methods used in, and results of, each review topic. After the description of research methods and the products of the literature searches, summaries of the six reviews are reported with conclusions and recommendations. The report finishes with a discussion of the study. This has resulted in some degree of duplication of text but with the aim of ensuring an appropriate level of detail throughout.

Chapter 2

Review methods for assessing effectiveness

Introduction

The methods of the review were based on those used by the Cochrane Collaboration⁹ and the Centre for Reviews and Dissemination.¹⁰ For identification, synthesis and presentation of the data on clinical effectiveness, the format of the Cochrane Collaboration was chosen. The principal reason for this decision was that the reviews were based on RCTs, and customised software (Review Manager) was available for the preparation and analysis of systematic reviews which incorporated statistical programs for meta-analysis, when appropriate.

Development of protocols

A review protocol was formulated for each of the six topics under review. The protocol structure followed that recommended by the Cochrane Collaboration.¹¹ Each protocol explicitly described:

- the objectives of the review
- the clinical and methodological criteria required of studies for inclusion
- the outcome measures of importance
- the search strategy to be used for identification of trials
- the methods of quality assessment, data abstraction and qualitative and quantitative synthesis of results.

Protocols were then lodged with the Centre for Reviews and Dissemination in York and entered into Review Manager. Completed protocols for the six topics form the background, objectives, and materials and methods sections of the reviews presented in appendices 4–9.

Search strategy for the identification of studies for inclusion in the systematic review

For the reasons outlined in chapter 1, the systematic search for studies of effectiveness was limited to finding RCTs. A broad search strategy was adopted in order to identify as many RCTs as possible relevant to the management of patients

with ESRD, and not only those relevant to the six review topics. This broad search served two purposes.

1. It avoided potential duplication of work which would have followed if separate searches had been performed for each selected topic.
2. It allowed the establishment of a register of RCTs relevant to the management of ESRD which we and/or others can use when performing future systematic reviews in this area. (A Cochrane Renal Review Group has recently been established and the register will contribute to the work of that Group.)

Systematic electronic bibliographic database searching

Five electronic databases were searched systematically:

- Medline (National Library of Medicine, USA: the electronic version of *Index Medicus*) using the search software Ovid, CD Plus
- Embase (Elsevier Science Publishers BV, The Netherlands: the electronic version of *Excerpta Medica*) using BIDS (on-line)
- CINAHL (CINAHL Information Systems, USA – Citation Index of the Nursing and Allied Health Literature) using the search software Ovid, CD Plus
- Biosis (Biological Abstracts Inc., USA: the electronic version of *Biological Abstracts*) using the search software SilverPlatter
- Cochrane Library (Cochrane Collaboration, UK: Update Software, April 1996; Issue 1, CD-ROM version – available from BMJ Publishing Group, London).

Medline was the first electronic bibliographic database to be searched. At this time, most search strategy development work by the UK Cochrane Centre had been carried out on Medline using SilverPlatter search software.¹² We modified this strategy for use on Medline (on Ovid, CD Plus) to allow for the different syntax used by the different search software.

The Cochrane search strategy has three components, each succeeding part being less specific but more sensitive than the one previous; the first is

relatively specific but insensitive, the last most sensitive but least specific. Pilot searches indicated that the third component did little to improve the number of relevant trials identified but generated very large numbers of abstracts describing studies using other types of research design; for this reason, we limited the search to the two initial components plus the textword search term 'volunteer\$' in title and abstract (as now recommended by the UK Cochrane Centre; 'volunteer\$' was the only term in the third part of the Cochrane search strategy that increased the number of RCTs identified without producing a large number of irrelevant abstracts). The Cochrane search strategy was combined with additional search terms describing the management of ESRD (see appendix 2). These were developed by a nephrologist and a research fellow experienced in literature searching, in line with the decision to perform a broad search covering all aspects of ESRD rather than perform individual searches for each of the review topics. These ESRD search terms were built up by investigating the MeSH terms, using the MeSH tree with scope notes and permuted index, as well as by textword searching (searching for terms in the title and abstract).

As new search terms were added to the search strategy, the first 50 references were scanned to assess their relevance to ESRD and dialysis; terms that retrieved only irrelevant articles were further modified or rejected. The final search strategy adopted for the Medline search is presented in appendix 2.

This search strategy was modified for searching other databases by changing the syntax to suit that of the relevant search software and interrogating the thesaurus or indices of each database to identify equivalents of the MeSH terms (i.e. the database controlled language). The definitive search strategies which were used to search Embase, CINAHL, Biosis and the Cochrane Library are also presented in appendix 2.

Other databases searched

The following databases were also searched. The search strategies are presented in appendix 2.

- Chemabs (Chemical Abstracts Service, USA: the electronic version of *Chemical Abstracts*) using STN. An on-line search, performed by a librarian experienced in use of this database, was focused on one of the review topics, acetate versus bicarbonate dialysate buffer.
- SIGLE (System for Information on Grey Literature in Europe, compiled by EAGLE) using

SilverPlatter, CD-ROM version. SIGLE was searched, in an attempt to identify RCTs in the grey literature in this field, by an experienced information officer at the Grampian Health Board.

- *CRIB (Current Research in Britain*, 10th edition, 1995; published by Cartermill Publications, London). This was searched in order to identify on-going trials in the field of dialysis and ESRD. Authors of on-going trials relevant to the six chosen topics were contacted to ascertain if the study was an RCT.
- NRR (National Research Register, 14th consolidation, September 1996). The aim was to identify on-going trials in the field of dialysis and ESRD. Authors of on-going trials relevant to the six topics were contacted to ascertain if the study was randomised.

Handsearching of specific journals

Experience of systematic reviews in other areas of health care has shown that despite rigorous searching of electronic bibliographic databases as in this review, a significant proportion of relevant RCTs are missed because of poor indexing.¹¹ Hence, a large number of journals are currently being handsearched as part of the Cochrane Collaboration's effort. The products of these searches are being made available through retrospective tagging in Medline and in the Cochrane Register of RCTs in the Cochrane Library. Any trials relevant to those reviews already found in this way by the Cochrane Collaboration should have been identified through the searches described above. Current handsearching, however, within the Cochrane Collaboration does not cover the majority of journals, particularly those in specialised areas. According to the Baltimore Cochrane Center, which coordinates handsearching activities worldwide, as of 6 May 1997, *Clinical Nephrology* and *Hellenic Nephrology* are the only nephrology journals currently being handsearched outside Aberdeen.

Only limited handsearching was possible within the resources available. *Kidney International* was chosen as the nephrology journal most likely to contain relevant RCTs; it is one of the main international nephrology journals and one of the most widely cited of all medical journals, and is held in the local medical school library. Full-text searching of *Kidney International* (including supplements) from January 1988 to December 1995 was therefore undertaken.

Each issue of *Kidney International* was fully searched and each original article found was read to the point where it was possible to make a definite classification of the study design. Conference abstracts,

with the exception of those listed in appendix 3) were not searched. This decision was taken after handsearching the conference proceedings for 1 year and extrapolating the figures over 15 years (approximately 9000 abstracts). For those abstracts relevant to the six topics, confirmation of subsequent publication and/or contacting authors for further details would have been required and it was decided that time and resources did not allow for this. Handsearching was performed by two members of the team, one a nephrologist and the other a methodologist.

A quality assurance control was implemented and a 'gold-standard' search was devised. The 1990 and 1995 volumes of *Kidney International* were searched by both handsearchers separately. After discussion an agreed attribution of all studies was made – this was the gold standard. A sensitivity and precision of greater than 90% was required of each searcher.

In keeping with the philosophy and practice of the Cochrane Collaboration, the aim of this handsearching was to identify all possible RCTs and controlled clinical trials (CCTs) regardless of subject content. Details of all such trials identified will be sent to the Cochrane Renal Review Group and to the Baltimore Cochrane Center, which is responsible for the Cochrane register of RCTs and for liaising with the National Library of Medicine for retrospective indexing on Medline.

Other methods of ascertainment of RCTs

Reference lists of selected articles

The reference lists of other reviews (expert/narrative), of identified RCTs and of relevant book chapters on the topics of interest were checked for possible RCTs. These searches were limited to 'first generation' references only; in other words, the reference lists of reports of studies originally identified from a previous reference list search were not searched (appendix 3).

Other experts in the field

The authors of trials included in each systematic review and those from whom clarification of methodology had been sought were contacted to ascertain if they knew of any other possibly relevant RCTs. An example of the letter and associated forms sent to authors is presented in appendix 10.

Biomedical companies

Where relevant, biomedical companies were contacted for details of any other relevant possible RCTs, published or unpublished.

Identification of possible RCTs

All possible RCTs were electronically imported or manually entered into the reference managing software package, Reference Manager (v. 6.01N, Research Information Systems, Carlsbad, CA, USA). Subject keywords and source of article were added.

Register of possible RCTs

All electronically derived abstracts and study titles were read by a team of three nephrologists to assess subject relevance. Initially, all abstracts were read by both a nephrologist and a methodologist; however, because of the high degree of concurrence, the greater speed at which the abstract could be assessed by the nephrologists and the large number of abstracts to be read (about 12,000), it was decided that the nephrologists alone should assess the abstracts. Each of three nephrologists was given up to 800 abstracts at a time and used a standard form (see appendix 10) to identify those abstracts judged to be possible RCTs or quasi-RCTs related to the management of ESRD. All possible RCTs or quasi-RCTs relevant to the six selected topics were assigned specific topic keywords on Reference Manager and the full published paper was obtained.

Quality assessment of studies

Full copies of studies were independently assessed for subject relevance, eligibility and methodological quality by a nephrologist and a methodologist using a standard form (see appendix 10). The quality of random allocation was recorded, including concealment of allocation, blinding, withdrawals, drop-outs, numbers lost to follow-up and whether intention-to-treat analysis was possible. The assessors were not blinded to author, institution or journal. Recent evidence suggests that blinding of assessors has a relatively small impact, if any, on the results of a meta-analysis.¹³ Any differences of opinion were resolved by discussion. If agreement could not be reached, a second double-assessor team, aware of the previous team's deliberations, reassessed the study and reached a final decision.

Data abstraction

A data abstraction form was generated for each review prior to the actual abstraction of the data from each published paper (see appendix 10). Only comparisons and outcomes that had been identified *a priori* in the protocols were included.

For each review, the data were abstracted by a single, medically qualified assessor and then entered into Review Manager.

Data analysis

Where results from studies could be quantitatively combined, a statistical meta-analysis of the data was undertaken to determine the typical effect size of the intervention. For dichotomous data, a 'typical' odds ratio (OR) was derived using Peto's method¹⁴ and, for continuous data, a weighted mean difference (WMD) was calculated (weighted by the inverse of the variance). Analyses for both dichotomous and continuous data adopted a fixed effects approach.¹⁵ Results from the limited number of included crossover trials were treated in the same fashion as parallel group trials.⁹

All comparisons were framed in terms of unfavourable events, such as adverse symptoms rather than freedom from adverse symptoms. As such, an OR

of less than one would favour the experimental treatment, and an OR greater than one would favour the control treatment. The 95% confidence intervals (CIs) were derived for all comparisons. Meta-analysis graphs have been presented when possible. An annotated example of such graphs is shown in *Figure 2*.

Evidence of heterogeneity¹⁶ across studies was explored using the chi-squared test for heterogeneity; if evidence of significant heterogeneity was identified, potential sources of heterogeneity were sought. If data could not be combined quantitatively they were assessed qualitatively.

Reporting

The reviews are reported in a modified form of the standard format of the Cochrane Collaboration (see appendices 4–9). The full reviews were then summarised for the purposes of this report (see chapter 4).

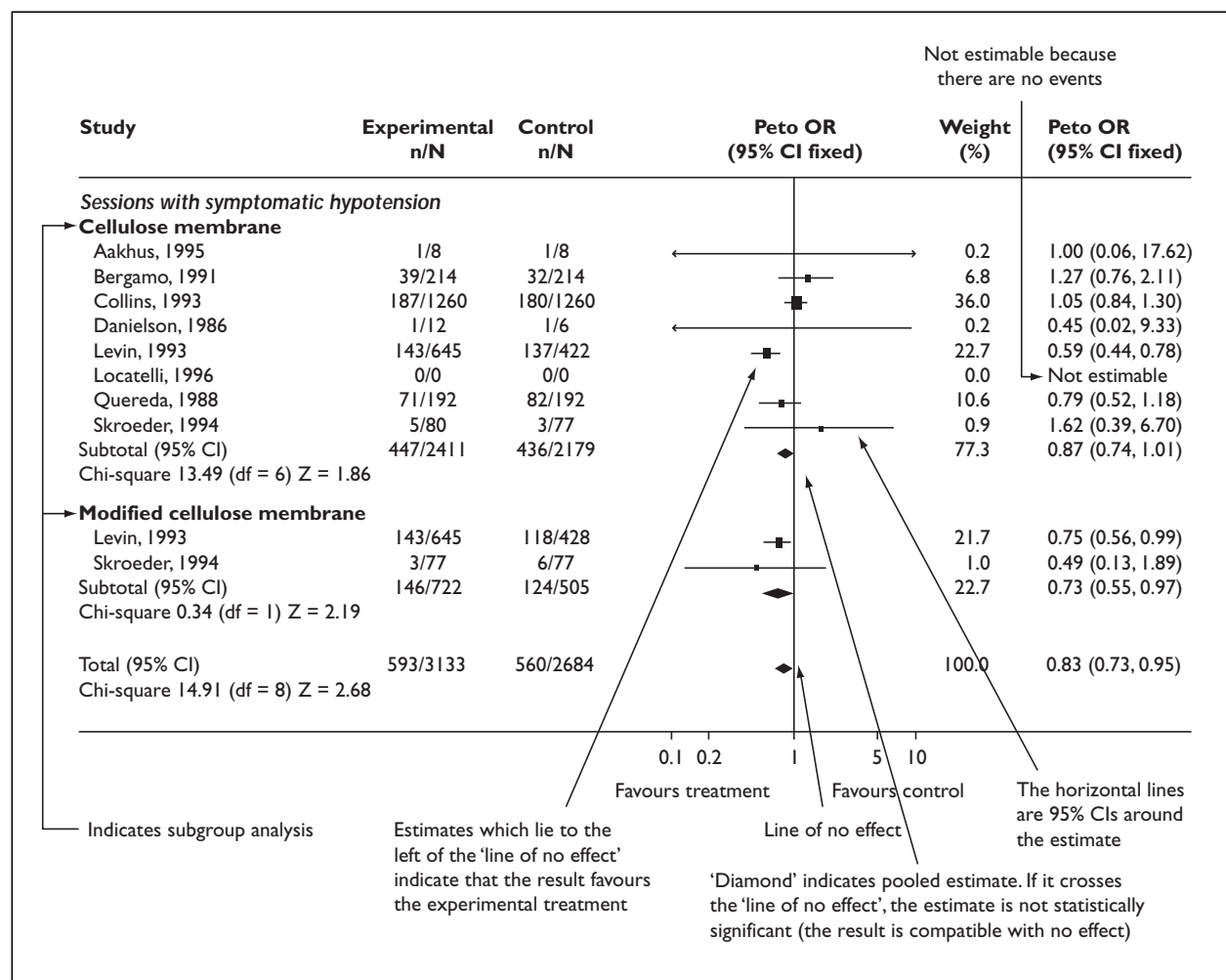


FIGURE 2 Example of meta-analysis graph (Comparison: synthetic vs. cellulose/modified cellulose haemodialysis membranes)

Chapter 3

Methods of economic evaluation

Introduction

Economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs (resource use) and effectiveness (health effects). In this study, the term 'alternative courses of action' can be equated to different ways of treating people with ESRD. Economic evaluation is useful for addressing both questions of technical efficiency and questions of allocative efficiency. Cost-effectiveness analysis deals with technical efficiency and has been defined by Mooney¹⁷ as the technique used to address the question of how to meet a given objective at least cost. Consideration of allocative efficiency means addressing the issue of how many resources to allocate to competing healthcare programmes. This involves making judgements about the relative sizes of different healthcare programmes and, therefore, about the relative worth of proposed expansions of such programmes. Such questions are addressed by cost-benefit analysis.

It may be possible to examine technical and allocative efficiency through cost-utility analysis (which has the advantage of focusing on the trade-off between cost and quality of life). However, we have used the more general frameworks of cost-effectiveness and cost-benefit analysis in decision-making because the nature of the evidence does not lend itself to estimating quality adjusted life-years – the main outcome measure used in cost-utility analysis.

The aim of the project was to address questions of efficiency as well as effectiveness of alternative approaches to dialysis. By deriving and linking estimates of the relative costs and effectiveness of the procedures under consideration, it

should be possible to determine whether one procedure is:

- (i) less costly as well as being at least as effective as its comparator, in which case it would be judged, unequivocally, to be a better use of healthcare resources (i.e. more technically efficient), or
- (ii) more costly, as well as more effective, than its comparator, in which case a judgement would have to be made about whether the extra cost is worth incurring in terms of the gains in health achieved (an allocative efficiency question).

The manner in which costs and outcome were related in this study is further developed as an economic framework.

The economic framework

The manner in which data on costs and clinical effectiveness can be brought together to aid in the judgement about whether one procedure should be preferred to a comparator is illustrated in more detail in *Table 2*. These theoretical permutations of cost and clinical effectiveness are brought together in a matrix in *Figure 3*.

For any procedure the optimum position on the matrix shown in *Figure 3* is the square A1, where an experimental treatment would both save costs and be more effective relative to a comparator. In squares A1, A2 and B1 the procedure is more efficient than a comparator and receives a positive response to the question of whether the experimental treatment is to be preferred. In squares B3, C2, and C3 the procedure is less

TABLE 2 Categories of evidence on effectiveness and cost

Cost	Effectiveness
A Evidence of cost savings	1 Evidence of greater effectiveness
B Evidence of no difference in costs	2 Evidence of no difference in effectiveness
C Evidence of greater costs	3 Evidence of less effectiveness
D Insufficient evidence to judge difference in costs	4 Insufficient evidence to judge difference in effectiveness

		Declining effectiveness →			
		1	2	3	4
↑ Increased cost	A	✓	✓	■	?
	B	✓	X✓	X	?
	C	■	X	X	?
	D	?	?	?	?

FIGURE 3 Matrix linking evidence on effectiveness and cost (✓ = yes, X = no; X✓ = neutral; ? = not enough evidence; ■, judgement required to be made.¹

¹ In economic terms this judgement about which treatment to choose in areas A3 and C1 involves the same trade-off; is the more effective treatment worth its extra cost? However, in practice it may be more difficult to justify the implementation of a lower cost but less effective alternative.

efficient than the comparator and this receives a 'negative response. In squares A3 and C1 a judgement is needed as to whether the more costly procedure is worthwhile in terms of extra effectiveness. Square B2 is neutral with no difference in either costs or effectiveness. In those squares with question marks there is insufficient information on cost or effectiveness or both to provide a definitive answer on relative efficiency.

Assessment of effectiveness

The methods used to assess the relative effectiveness of the interventions being compared were described in chapter 2.

Identification of data on resource use and cost

Data collection

Two ways of identifying data on resource use and costs were considered. The first was a broad search for relevant studies conducted in parallel with the searches for RCTs of effectiveness. The second was a more focused search, delayed until the reviews of effectiveness had been completed, aimed at supplementing economic information from the RCTs. The former approach was chosen for two reasons. Firstly, it was anticipated that RCTs would probably not be the best source of information on resource use and that each individual trial would

not have incorporated a formal economic evaluation. Secondly, it was predicted that the reviews of effectiveness would take most of the time available, leaving insufficient time for any later searching of the economics literature. As a result, a separate, parallel search strategy of electronic databases was developed which attempted to identify the maximum number of economic evaluations and studies that considered the resources used in the management of ESRD relevant to the six review topics. The strategy was developed by the health economists and a research fellow experienced in literature searching. This strategy did not confine itself to randomised or quasi-randomised CCTs, unlike the search on effectiveness, but included economics studies using other research designs.

Although the detail of each review is slightly different, in general, data from the systematic reviews of trials were used:

- to assess relative effectiveness
- to estimate resource use associated with the initial interventions
- to estimate the resource consequences, if any, of differential rates of adverse events (such as complications).

Data from additional material identified in the review of economic studies were used:

- to estimate differential rates of adverse events with resource consequences, when such data were not available from the review of RCTs
- to provide estimates of the magnitude of resources used in each option evaluated, when such data were not available from the review of RCTs (although if more accurate estimates could be obtained from local, that is, UK-based, costings, these were used instead).

Databases searched for the review of economic studies were:

- Medline
- Embase on BIDS
- CINAHL
- Biosis
- IBSS (British Library of Political and Economic Science) using BIDS
- NEED (NHS Economic Evaluation Database, NHS Centre for Reviews and Dissemination) on-line
- Econlit (American Economics Association) using the search software SilverPlatter
- *The Economist* (The Economist Newspaper Ltd, London) on CD-ROM.

Details of the years searched and the search terms are presented in appendix 2.

The Medline search strategy was the first to be developed using similar methodology to that for the electronic search for possible RCTs (see chapter 2). The search terms to identify RCTs were omitted in this search strategy. These terms were replaced by terms designed to identify economic evaluations and studies that considered the resources used in the management of ESRD. The Medline search strategy was then modified for searching other databases (see chapter 2).

Identification of potentially relevant studies and economic evaluations from titles, abstracts and keywords

The abstracts generated by the search for additional papers relevant to the economic evaluation were assessed by one health economist. This followed a pilot exercise in which no differences were found in the abstracts selected when they were read by two health economists. All possible studies that were potentially relevant to the economics of the management of ESRD were identified using the same standard form (see appendix 10) used in the identification of possible RCTs or quasi-RCTs. These reports were assigned, where appropriate, to our six specific topic files and the complete published paper was obtained.

Quality assessment

Using a similar methodology to that described for the systematic review of effectiveness, the methodological quality of identified studies was assessed by one health economist (see the economic quality assessment form in appendix 10).

Data abstraction

A single investigator abstracted data on the characteristics of participants, interventions and outcome measures from each economic

evaluation, study, RCT or quasi-RCT. The precise data abstracted depended on the topics. In general, information about resource use was abstracted on the dialysis treatments described, taking into account their duration and frequency, incidence of complications, treatment of complications, time delay before complication occurs, duration of complication and duration of the treatment of complications.

When data were required on items of resource use (i.e. labour, consumables or capital) and on the occurrence of events with resource consequences, they were abstracted, if possible from the included RCTs. When this was not possible, information was abstracted from the less rigorous studies identified by the separate economic searches.

Data analysis

The objective of the data analysis was to combine data on differential resource use with data on effectiveness obtained from the systematic review of RCTs of effectiveness. Data were analysed in two stages. First, when economic evaluations were identified which attempted to address the study questions, their methods were evaluated and their results synthesised. Second, the results of the systematic literature search for studies that reported data on resource use were combined with the data on effectiveness obtained from the systematic review of RCTs described above. For all reviews, except for the comparison of CAPD and haemodialysis, the information on resource use and cost was combined to assess relative efficiency using a decision-analysis approach (this is described in detail in appendices 4–9). For the comparison of CAPD with haemodialysis, the data from formal economic evaluations conducted by others was synthesised.

All costs are presented in £UK for the financial year 1996/97.

Chapter 4

Summary of results

Systematic literature review

Over 12,000 abstracts of published papers were considered for inclusion in the review of effectiveness. *Table 3* summarises:

- where they were first identified
- how many were judged to be possible RCTs relevant to ESRD
- how many of these were concerned with the chosen six topics
- how many were confirmed to be RCTs suitable for inclusion
- how many were considered in the economic analysis.

Full details are presented in appendix 3.

Results of searches for RCTs for assessing effectiveness

The search identified 537 studies as possible

RCTs relevant to the topics under review, of which four were conducted in the UK. However, after assessment of the full published papers of these studies, only 47 were found to be RCTs in which any of our predetermined outcome measures for one or more of the reviews had been considered. Of these, 34 were found on Medline after reading 5429 abstracts, a further five were found among the 6447 abstracts generated by the systematic searches of the other electronic databases, and the remaining eight were found by other means.

Results of economic searches

In the supplementary health economics electronic searches, a total of 4168 abstracts, additional to those from the effectiveness search were assessed. For 820 of these, full papers were ordered as they appeared likely to contain information. Most of these papers were used either to clarify the issues around the six questions or for reference

TABLE 3 Sources of RCTs included in the reviews

Source	Number of reports identified ^a	Number of possible RCTs relevant to ESRD ^b	Number of possible RCTs relevant to topics ^{b,c}	Number of RCTs included in final review
Medline	5429	1480	243	34
Embase	4764	391	81	4
CINAHL	366	25	10	0
Biosis	1317	189	4	1
Cochrane Library	N/A ^d	N/A ^d	2	0
Subtotal (systematic electronic searches)	11,876	2085	340	39
Other databases ^e	269	122	9	0
Handsearching	287	133	48	0
Reference lists and experts in the field	56 ^f	N/A ^g	140	8 ^h
Subtotal (all other sources)	612	255	197	8
TOTAL	12,488	2340	537	47

^a Some reports were identified from more than one source

^b Includes controlled trials with quasi-random methods of allocation

^c Relevant to the six selected topics

^d A nephrologist searched this database on-screen and selected RCTs/CCTs relevant only to the six topics (for search strategy see appendix 2)

^e Chemabs, SIGLE, CRIB, and NRR

^f Numbers of reference lists checked

^g Collected possible RCTs for the six topics only

^h Responses from the authors of RCTs and CCTs are currently being assessed; any additional RCTs will be incorporated into later versions of the Cochrane systematic reviews. Five RCTs came from reference lists and three from experts in the field

when developing the methodology to address each question.

Discussion

Although the aim was a highly sensitive but relatively non-specific search strategy, we were still surprised by the number of reports identified. In respect of RCTs alone, approximately 12,000 abstracts were assessed and this represented a major undertaking with significant resource implications for the project group. From our prior knowledge of the field, we did not expect to find many RCTs. Although the dividend of only three RCTs per 1000 abstracts assessed seems disappointing, the total number of relevant RCTs identified (47) is somewhat greater than was expected. However, as described later, the RCTs tended to be small and of variable quality.

About 70% of relevant RCTs were identified from the Medline search, which is consistent with experience in other fields. It confirms that the decision to search Medline first was correct. The next greatest yield was from Embase but only about one extra RCT was found for each 1000 abstracts checked.

The decision to carry out a broad search for economic studies at the beginning of the review period also resulted in the assessment of large numbers of additional papers. However, the time taken to complete the reviews of effectiveness was longer than expected, and allowed no time later for the more focused economics searches that had been initially considered.

In the light of our experience, one option in future economic evaluations would be to perform a restricted literature search at the beginning of the review period, and supplement this by further focused searches to address any outstanding gaps once the effectiveness reviews have been completed.

Review 1: Comparison of synthetic with cellulose and modified cellulose membranes in the haemodialysis of patients with ESRD

The full systematic review is presented in appendix 4.

Background

The basic principle of haemodialysis is that products of protein breakdown and water can be removed when blood is passed over a semi-

permeable membrane in a dialyser with dialysate flowing on the other side. Metabolites are removed mainly by diffusion and water by the application of a pressure gradient across the membrane. Cellulose-based membranes, produced principally from cotton, were the first membranes produced for dialysis and, in their standard form, have a low hydraulic permeability (low flux). Characteristically, they also have poor clearance of molecules larger in size than urea and creatinine, and this may be responsible for some of the clinical features of uraemia. Because of their poor clearance of β_2 microglobulin, it is thought that amyloid disease may occur more frequently in patients treated with these membranes. This condition is characterised by carpal tunnel syndrome, bone and joint disease; it rarely occurs during the first 5 years of dialysis but by 12 years it affects 50% of patients.

In recent years standard cellulose membranes have been modified to make both larger molecule and water removal more efficient; that is, they can be manufactured to have a higher flux than was possible with standard cellulose membranes; such membranes are called modified cellulose, substituted cellulose or semi-synthetic membranes. In general, they are more expensive than standard membranes although this may now be changing.

In the early 1970s, synthetic polymer-based membranes became available. They are usually manufactured with high-flux characteristics but can also be manufactured to have a low flux. They may remove β_2 microglobulin, which may cause dialysis-related amyloid disease, more effectively, especially those which have high-flux characteristics. It is of particular importance to evaluate the benefits of the synthetic membranes. Although high-flux properties may be better, they are generally about three to four times as expensive as cellulose or modified cellulose membranes. Despite the economic and practical importance of the choice of dialysis membrane, the benefits of synthetic membranes are not clear to nephrologists or to healthcare planners and, if benefits do exist, can their extra costs be justified.

Objective

The objectives of the study were:

- to determine whether good evidence supports the view that synthetic membranes offer clinically important advantages compared with standard cellulose or modified cellulose membranes in the haemodialysis of patients with ESRD
- to determine from the literature the resource-use implications and relative efficiency analysis of the use of synthetic membranes.

The hypotheses being tested were that using synthetic membranes (compared with cellulose or modified cellulose membranes):

- (i) reduces the frequency of adverse symptoms during dialysis (symptomatic hypotension, headaches, nausea and vomiting, pruritus and anaphylaxis)
- (ii) reduces the number of significant infections and hospital admissions (including length of stay)
- (iii) improves dialysis adequacy, as measured by Kt/V or urea reduction ratio (URR)
- (iv) decreases predialysis β_2 microglobulin values and the incidence of amyloidosis
- (v) improves the patient's lipid profile
- (vi) improves predialysis albumin and protein catabolic rate (PCR)
- (vii) improves quality of life and patient survival.

Methods

Search strategy, inclusion criteria and methods of the review are described in chapters 2 and 3 and appendices 2 and 4.

Results

The inclusion criteria were met by 22 studies; data from these were summated by meta-analyses – Peto's OR and WMD – and 22 outcome measures were sought. For two outcome measures, number of episodes of significant infection per year and quality of life, no data were available and for one, URR – a measure of dialysis adequacy – data were not given in a form that could be analysed. For the comparison of cellulose with synthetic membranes, data for 10/19 outcome measures were studied in only a single trial. For modified cellulose and synthetic membranes, 4/7 outcome measures were each assessed in one trial only and for 12 of the outcomes no trials were found.

The incidence of nausea and vomiting was significantly less with synthetic than with cellulose membranes (OR, 0.62; 95% CI, 0.49, 0.78). Predialysis β_2 microglobulin concentrations were significantly lower at the end of the studies in patients treated with synthetic membranes, although all studies which showed this effect used high-flux synthetic membranes (WMD, 14.5; 95% CI, 17.4, –11.6).

Similarly, one study showed that the incidence of amyloid was less in patients who were dialysed for a period of 6 years with high-flux synthetic membranes; no low-flux membranes were used in this study (OR, 0.05; 95% CI, 0.01, 0.18). Plasma triglyceride values were lower with synthetic membranes (high-flux) in the single study that

measured this outcome (WMD, –0.660; 95% CI, –1.181, –0.139). Serum albumin was also higher in patients treated with synthetic membranes (WMD, –0.111; 95% CI, –0.210, –0.013).

It is therefore difficult to determine whether the differences found were attributable to the materials from which the membranes were made or to the differences in flux. There was no significant difference between these membranes for any of the other clinical outcomes measures.

Pruritus occurred less frequently with synthetic membranes than modified cellulose membranes (OR, 0.78; 95% CI, 0.66, 0.93); no other differences were found. The differences between synthetic and modified cellulose appeared smaller, although many fewer trials were carried out for this comparison. Economic evaluation showed that these additional benefits for synthetic membranes were achieved at considerable cost.

Conclusions and implications

Policy implications

The authors are hesitant to recommend the universal use of synthetic membranes for haemodialysis in patients with ESRD on the basis of the above results because of the small number of trials (many with low patient numbers), the heterogeneity of many of the trials compared, the variations in membrane flux and the differences in exclusion criteria, particularly co-morbidity. There is insufficient information from this review to carry out a satisfactory economic evaluation. Such evidence as there is favours synthetic membranes over cellulose membranes but if extra benefit is assumed it would be at considerable cost, particularly if high-flux membranes were to be used. In particular, little evidence was found of any difference between synthetic and modified cellulose membranes. However, the price of high-flux membranes is likely to change in the future; hence, policy recommendations should be kept under review.

Future research needs

Further RCTs are required to compare the different dialysis membranes available.

They are required to:

- (i) take into account reuse of membranes and other properties, particularly flux, as well as the material from which the membrane is made, and should include modified cellulose membranes and low-flux synthetic membranes which are less expensive than their high-flux counterparts

- (ii) record the minimum of data concentrating on primary outcomes of major importance to patients
- (iii) explicitly record whether the symptoms used as outcome measures are patient or staff reported, while recognising that, in general, patient-reported data will be more appropriate for evaluating effectiveness but staff-reported data may be necessary for calculating the cost of treating complications
- (iv) be multicentre (and possibly multinational) in order to have sufficient patients to complete the study and allow for withdrawals and drop-outs
- (v) have sufficient length of follow-up to draw conclusions about important clinical outcome measures and continue to follow-up patients who have undergone transplantation
- (vi) include older patients and those with co-morbid illnesses, and take age and co-morbidity into account when assessing outcomes (possibly by stratification at trial entry)
- (vii) carry out an economic evaluation.

Review 2: Comparison of bicarbonate-buffered with acetate-buffered dialysate in haemodialysis as treatment for patients with ESRD

The full systematic review is presented in appendix 5.

Background

Bicarbonate has largely replaced acetate dialysate in the haemodialysis of patients with ESRD in the UK, on the assumption that it significantly reduces intradialytic adverse symptoms and improves haemodynamic stability.

Objective

The objective of this review was to compare bicarbonate with acetate haemodialysis in patients with ESRD and to assess whether there is evidence of improved patient outcome to support its adoption as the dialysate of choice. The cost implications of using bicarbonate haemodialysis instead of acetate haemodialysis were also to be examined. The hypotheses being tested were that bicarbonate haemodialysis:

- (i) reduces the frequency of adverse symptoms during dialysis compared with acetate haemodialysis

- (ii) improves cardiovascular stability during dialysis compared with acetate haemodialysis
- (iii) improves the patient's lipid profile compared with acetate haemodialysis
- (iv) slows the progression of renal bone disease compared with acetate haemodialysis.

Methods

Search strategy, inclusion criteria and methods of the review are described in chapter 2 and in appendices 2 and 5.

Results

The inclusion criteria were met by 18 studies and data from these studies were synthesised using meta-analyses. There was a significant reduction with bicarbonate dialysis in the number of haemodialysis treatments complicated by headaches (OR, 0.84; 95% CI, 0.71, 0.99), nausea/vomiting (OR, 0.42; 95% CI, 0.26, 0.66), symptomatic hypotension (OR, 0.28; 95% CI, 0.11, 0.69) and non-specific intolerance (OR, 0.79; 95% CI, 0.67, 0.93). There was a lack of clear evidence of benefit from bicarbonate dialysis in terms of improved cardiovascular stability, lipid profile and indicators of renal bone disease.

Conclusions and implications

Policy implications

1. Bicarbonate dialysis is preferable to acetate dialysis for the haemodialysis of patients with ESRD because of its associated reduction in intradialytic adverse symptoms and similar cost.
2. In those countries with less well-financed renal replacement services, who continue to depend on haemodialysis machines that can only use acetate dialysate, replacement of their machines with those that can use either dialysate should be encouraged as replacements are required. However, the cost to their healthcare systems of a complete rapid change to new dialysis machines or modification of all their present machines would not be warranted on the basis of the relatively modest benefits which bicarbonate dialysis offers. The benefits of such changes need to be considered in terms of their opportunity cost and this will vary from country to country. The provision of information on the costs and benefits of such a change provided in this review should assist in the estimation of such opportunity costs.

Future research needs

Methodologically sound clinical trials with long-term follow-up comparing bicarbonate with acetate haemodialysis are rare. We should continue to

be open-minded about the possible beneficial or adverse effects that bicarbonate dialysis may have on long-term outcomes such as lipid profile and cardiovascular disease, renal bone disease and morbidity.

Any further RCT at this stage is unlikely to produce significantly different data from that which exists already and is therefore unlikely to change clinical practice.

Review 3: Comparison of short duration with standard duration haemodialysis as treatment for patients with ESRD

The full systematic review is presented in appendix 6.

Background

Shortening haemodialysis treatment time is welcomed by the patient and is seen by the health-care purchaser as an improved use of resources. Technological advances, coupled with patient pressure and pressure on costs, led to the development and implementation of shortened dialysis schedules, particularly in the USA. However, the annual mortality among dialysis patients in the USA began to increase as the average dialysis treatment times decreased. If short dialysis is at least comparable to standard dialysis in terms of clinical outcome, it should be offered to all appropriate patients. If, however, it has significant disadvantages compared to standard dialysis, either in the short or long term, those patients to whom it is being offered should be made aware of the potential trade-off.

Objective

The objective of this review is to ascertain the effect of short haemodialysis treatment duration (> 3.5 hours) on patient morbidity and mortality, assuming a treatment frequency of three per week. It also attempts to assess patient preference and the impact of shortened treatments on healthcare resource use.

Methods

Search strategy, inclusion criteria and methods of the review are described in chapters 2 and 3 and in appendices 2 and 6.

Results

Only a single study by Lowrie and colleagues (1983) with 165 randomised patients was identified.

There was no significant difference in mortality (OR, 0.53; 95% CI, 0.05, 5.15). Morbidity as reflected by hospitalisation rates was greater in the short-duration dialysis group (OR, 2.85; 95% CI, 1.39, 5.85). There was no conclusive difference in the incidence of intradialytic adverse symptoms between the groups. Blood pressure control was worse in the short-duration dialysis group as indicated by predialysis systolic blood pressure (mean difference, 7.5 mmHg; 95% CI, 3.1, 11.8), predialysis diastolic pressure (mean difference, 2.9 mmHg; 95% CI, 0.5, 5.2), and predialysis mean arterial blood pressure (mean difference, 3.4 mmHg; 95% CI, 0.0, 6.9).

Conclusions and implications

Policy implications

1. Current evidence from this North American study offers little reassurance that short-duration dialysis (≤ 3.5 hours, three times per week) is as effective as standard dialysis. There is no evidence that reduced dialysis duration improves patient outcome in terms of mortality and morbidity. It may, in fact, increase morbidity as reflected by increased hospitalisation and poorer blood pressure control. From this it is concluded that 'standard' dialysis duration (> 3.5 hours, three times per week) should remain the recommended treatment. It should be noted that no study was found that compared the longer duration dialysis that is the norm in Europe.
2. If a reduced dialysis duration regimen is implemented on the basis of patient preference or assumed lower cost, its unproven safety should be explicitly acknowledged.

Future research needs

1. One or more large, multicentre, pragmatic RCTs comparing haemodialysis treatment duration policies are required. Such a trial should include the longer duration haemodialysis practised in Europe, have minimum exclusion criteria, a long follow-up period and minimum data collection that concentrates primarily on patient morbidity and mortality. The follow-up should include patients who withdraw (for example, for renal transplantation) and all patients should be followed for a period after trial completion to assess residual effect on mortality and morbidity. Key primary outcomes such as mortality should be analysed on an intention-to-treat basis. Avoidance of collection of secondary outcome data should reduce the complexity of such a trial. Dialysis therapy and the overall treatment of ESRD within such a trial should be to the highest

standard as recommended by the best available evidence.

2. If such a trial showed no advantage with standard duration dialysis, short-duration dialysis should be the recommended treatment option.
3. The HEMO RCT, comparing high- and low-flux membranes and the ability to achieve a given Kt/V, is at present under way. It may address some of the above questions. This should be taken into account when the research agenda is decided.

Review 4: Comparison of CAPD delivery systems – Y-set/modified Y-set versus standard spike as treatment for patients with ESRD

The full systematic review is presented in appendix 7.

Background

CAPD is an alternative to haemodialysis for patients with ESRD. It may be used as the first choice therapy and, in a number of countries, more patients are treated by this modality of treatment than by haemodialysis. Catheter and transfer set types, insertion techniques, and peri- and post-operative management display significant variation.

There are two main types of catheter connecting systems:

- (i) the standard or straight connecting system in which the catheter is connected with a straight piece of tubing, which in turn is connected to the dialysate bag. At each exchange the bag is drained and a new connection is made. The empty bag is rolled up and remains attached until the next exchange when the process is repeated
- (ii) the Y-set in which the patient is disconnected from bags between exchanges and, when a new exchange is due, a Y-connection is used, with one limb connected to an empty bag and one to a bag containing fresh dialysate. The peritoneal dialysate is first drained into the empty bag. Before introducing the new fluid, the Y-connector is flushed with fresh dialysate into the drained bag, which allows any bacteria to be flushed into the spent fluid. The fresh fluid is then introduced into the peritoneal cavity and the connector removed from the catheter.

At present about 40% of CAPD patients in the UK use this connecting system (data from the

National Registry provided at the Renal Association meeting, 1997).

Objective

The aim of this review is to describe the best practice for CAPD-connecting systems, insofar as present evidence allows, and to indicate where future research should be concentrated.

The hypothesis being tested was that the Y-connector/modified Y-connector was associated with fewer episodes of peritonitis than the standard connector in patients on CAPD.

Methods

Search strategy, inclusion criteria and methods of the review are described in chapters 2 and 3 and in appendices 2 and 7.

Results

Six studies met the inclusion criteria and results of these studies were synthesised using meta-analysis.

The Y-set/modified Y-set significantly reduced the incidence of CAPD-related peritonitis compared with standard non-Y-set connection systems. There was no difference in the incidence of exit-site infections between the two methods.

The number of patients who experienced at least one episode of peritonitis in all the studies combined was significantly lower in patients using the Y-set delivery systems (57/194 versus 107/201; OR, 0.30; 95% CI, 0.23, 0.53) compared with those assigned the non-Y-set system. Only one study (Cheng, *et al.*, 1994 – see appendix 7) did not show this effect, although all studies demonstrated a significant increase in the number of months per episode of peritonitis. No study provided standard deviations for this statistic and, hence, a WMD could not be obtained. All studies also showed that the time to first peritonitis was longer with the use of Y-set/modified Y-set systems.

There was no evidence of significant reduction in the number of patients who suffered exit site infection or tunnel infections with the Y-set (39/162 versus 44/171; OR, 0.87; 95% CI, 0.51, 1.48).

Conclusions and implications

Policy implications

Peritonitis is one of the main complications of CAPD and is known to lead to morbidity, technique failure and mortality. Based on the results of this review, there is insufficient evidence to support the continued use of non-Y-set connecting systems in CAPD. The economic evaluation of this review

reveals that the use of a Y- or modified Y-set connector imposes an incremental cost of approximately £900 to £3900 per patient per year, based on low and high cost estimates. Preventing one episode of peritonitis would cost approximately £4700 per case of peritonitis avoided. However, there was wide variation in this estimate, which depended on the relative probability of peritonitis episodes.

The Y-set delivery system significantly reduces the incidence of peritonitis. Given that recurrent peritonitis is a major cause of technique failure, the additional cost is likely to be justified.

Future research needs

Peritonitis remains a major problem in CAPD and further research into methods of prevention of this complication is required.

Evidence of the effect of technique failure on patient outcomes and costs would further inform the evidence concerning the use of Y-set systems.

Review 5: Comparison of CCPD with CAPD as treatment for patients with ESRD

The full systematic review is presented in appendix 8.

Background

CAPD is an alternative to haemodialysis for patients with ESRD. Dialysate fluid is drained into and then out of (exchange) the peritoneal space using a surgically-placed permanent catheter in the abdominal wall. These exchanges are performed four times daily. One of the major complications of the technique is peritonitis. CCPD is a modification of this technique in which exchanges are performed overnight by a machine and it has recently been proposed as an alternative for all patients suitable for chronic peritoneal dialysis. It has also been suggested that it may decrease the incidence of peritonitis.

Objectives

The objectives of this study were to undertake a systematic literature review comparing CCPD with CAPD, while testing the following hypotheses with which CCPD is associated:

- (i) reduced incidence of dialysis-associated infections
- (ii) improved adequacy of dialysis
- (iii) reduced incidence of technique failure
- (iv) increased patient preference for the technique (compared with CAPD).

Methods

Search strategy, inclusion criteria and methods of the review are described in chapters 2 and 3 and in appendices 2 and 8.

Results

Only a single study involving 82 patients met the inclusion criteria. Results are expressed as ORs and WMDs. There were no significant differences in the number of patients with peritonitis (OR, 0.56; 95% CI, 0.24, 1.33), catheter exit-site infections (OR, 1.13; 95% CI, 0.43, 2.94) or catheter-tunnel infections (OR, 0.5; 95% CI, 0.05, 4.99). However, when infective complications were reported as episodes per patient year, the study demonstrated a reduced mean incidence per patient year of peritonitis – CCPD, 0.51; CAPD, 0.94 ($p = 0.03$). There was no significant difference in measures of dialysis adequacy, such as Kt/V (WMD, 0.40; 95% CI, -0.23, 1.03) and 6-monthly serum creatinine, urea and phosphate. Though fewer patients on CCPD needed to change dialysis technique this was not statistically significant (OR, 0.48; 95% CI, 0.18, 1.26).

Because this was a parallel group trial design, patient preference could not be adequately assessed. We estimated that the cost per episode of peritonitis avoided by using CCPD was £21,000.

Conclusions and implications

Policy implications

The review indicated that CCPD showed benefit for one patient outcome but is more expensive than CAPD. The authors suggest that, at present, CCPD is offered to patients for whom there is a specific indication. However, patient preference is likely to be important here.

Future research needs

1. Further RCTs are required which compare CCPD with CAPD with particular reference to peritonitis, technique failure rates and patient preference. If these confirm the reduced peritonitis rate of CCPD, then it may need to be considered as the preferred chronic peritoneal dialysis option.
2. More widespread use of CCPD may have significant resource-use implications. Future RCTs should include a thorough economic evaluation to provide more information on whether any additional benefits are worth the additional resources that CCPD, relative to CAPD, may require.

RCTs and economic evaluations are required to compare CCPD with haemodialysis to determine whether it is efficient to provide CCPD for those patients who have a relative contraindication to CAPD and would otherwise be treated by haemodialysis.

Review 6: Comparison of haemodialysis with CAPD as treatment for patients with ESRD

A full systematic review is presented in appendix 9.

Background

Patients with ESRD require either dialysis (haemo- or peritoneal dialysis) or renal transplantation to maintain life. Transplantation is normally considered to be the preferred choice but there are insufficient donors to meet the demand. Therefore, for those patients for whom transplants are unavailable or who are unsuitable for transplantation, there is the question of which mode of dialysis should be used.

Objective

The objective was to ascertain if there is clear evidence for the increased effectiveness of haemodialysis compared with CAPD for all patients with ESRD, or a particular subgroup of patients with ESRD. It was also the aim to ascertain the relative costs of haemodialysis and CAPD and to combine this information with the information on effectiveness to determine which of these modalities is the more efficient.

Methods

The methodology used to answer this question is described in detail in chapter 3. In addition, the systematic review of 'economic aspects' identified formal economic evaluations that had tried to assess the relative efficiency of CAPD and haemodialysis. The results of these economic evaluations were summarised to provide an overall view of the current evidence of the relative efficiency of these two modes of treatment.

Results

No RCTs were identified that compared CAPD with haemodialysis. The economic evaluations identified made assumptions on the basis of data from poor quality study designs that CAPD is cheaper than haemodialysis and, in some cases, that haemodialysis provides better patient survival. Because of the poor quality of the study designs used to obtain primary data, it is not possible to

judge whether the assumed extra benefits provided by haemodialysis are worth any extra costs that may be incurred.

Conclusions and implications

The issue facing the health service is not whether to have CAPD or haemodialysis but rather the balance of provision between the two modalities. We know from variations in uptake of these techniques in different countries that a large proportion of patients requiring dialysis for ESRD could be managed with either CAPD or haemodialysis initially. What is required is information about the relative costs, benefits and risks of policies of starting with one or other modality. In this respect, it should be possible to develop a more detailed model based upon observational data. Ideally, information on benefits and risks should come from comparisons, within a pragmatic RCT, of policies based on starting with CAPD or haemodialysis, as used in the UK.

Data are not available to allow reliable conclusions to be drawn about the relative effectiveness and efficiency of haemodialysis and CAPD.

If an assumption is made of equal effectiveness in terms of survival then the limited data available favour CAPD.

Although some studies have assumed that a policy of starting with haemodialysis is more effective than a policy of starting with CAPD, it is not possible to quantify reliably with current data this extra benefit and, hence, it is not possible to determine whether haemodialysis is worth any extra cost that may be incurred. This issue would be resolved most reliably by a pragmatic RCT that includes a formal economic evaluation comparing the two policies. Currently, Baxter Ltd are attempting to undertake a RCT in this area (Personal communication, 1997).

The implications of policies based on starting with haemodialysis rather than on CAPD are more complex than described in previously reported economic evaluations. An attempt at a more sophisticated economic model is described in appendix 9. The results obtained using this model are, however, inconclusive, because of the poor quality of the data.

The development of new methods of dialysis, such as CCPD, and the advances in renal transplantation techniques warrant additional evaluation to investigate their place alongside haemodialysis and CAPD in the treatment of ESRD.

Chapter 5

Discussion

The management of ESRD was one of the first priorities identified in the NHS R&D Health Technology Assessment Programme. The original 1994 commissioning brief, which led to the work reported here, called for a systematic review of ESRD, “concentrating on the effectiveness and cost-effectiveness of alternative schedules of conventional haemodialysis and CAPD”. Given the complexity of the issues involved, and the limited time and resources available, we chose to concentrate on what were judged to be key ‘decision points’ in the management of ESRD. The choice was made after developing a dialysis decision tree (see *Figure 1*) and six topics were selected. There are, therefore, many aspects of the management of ESRD which are not addressed directly in this study (although an attempt was made to consider some of these, such as co-morbidity, indirectly). This is not then a comprehensive systematic review of the management of ESRD.

The reviews were performed systematically in the sense that there were explicit search strategies, explicit selection criteria for the studies considered, explicit data extraction protocols and explicit methods for data synthesis. In other words, it would be expected that repetition of this study would be likely to lead to similar findings. The reviews were not, however, comprehensive in the sense that all types of evidence were considered. It was judged that protection from the distorting effects of selection and other biases was likely to be most secure if our reviews were limited to RCTs and so other study designs were not considered systematically (other than in the review of economic analysis of haemodialysis compared with CAPD). When this decision was taken, we were aware of the argument that some well-conducted non-randomised cohort studies may be less prone to bias than poor quality RCTs. Nevertheless, it was decided that it was important to identify and assess all RCTs first; also, we realised that we did not have the resources to identify studies using other research designs systematically, partly because of the work involved in finding the RCTs and partly because the methods for finding well-conducted observational studies are not well developed.

In an attempt to avoid duplication of effort, a broad search for RCTs related to the management of ESRD in general was undertaken rather than

searches restricted to just the six topic areas formally covered. We were fortunate to be able to draw on the search strategy developed for this purpose by the Cochrane Collaboration, although this did need extensive adaptation for use on databases other than Medline. The aim was for a sensitive search to identify as complete a register of relevant trials as possible. In retrospect, the size of this task was underestimated, particularly in respect of the relatively poor specificity that this decision implied. In the event, about 12,500 abstracts were assessed (see *Table 3*) in order to identify the 47 RCTs considered in the six reviews.

Despite these efforts, it is possible that a few relevant RCTs have not been included: non-English language databases were not searched; ‘grey literature’ has been covered to only a limited extent; Science Citation Index has not been fully used; the Internet has not been fully explored, and hand-searching has been limited. It is difficult to estimate how many relevant RCTs may have been published in non-English language journals or are non-European based RCTs missed in the searches; no language limits were used when searching the electronic databases and, where possible, non-English papers were translated to clarify, first, if they were RCTs and, second, if they were relevant to the six topics (so far only nine possible RCTs identified from the searches have not been translated; 22 papers were translated). It has not been possible to estimate the size of the renal literature in, for example, Japan (where the Cochrane Stroke Group found 25% of its RCTs); a search of Medline (1993–November 1997) found almost 3000 possible RCTs related to ESRD and dialysis, of which 47 were in Japanese and a further 149, in languages other than Japanese, were by authors based in Japan. Contact with the authors of the one Japanese study included in the reviews and with other authors based outside Europe did not identify any new relevant RCTs in any language. Also, responses are still being received from authors of abstracts and articles clarifying their study methodologies and suggesting other possible RCTs; hence, it has not been possible to consider these here. It was partly for this reason that the reviews were written using the Cochrane format. This will allow them to be updated easily as and when further RCTs are identified.

We were fortunate to be given access to all the resources of the Cochrane Collaboration at a time when there was no formal Cochrane Renal Group. (This was subsequently established in 1997 with one of us, Alison MacLeod, as an editor.) The use of the customised software, Review Manager, made the task much easier, with the one limitation that some forms of data, such as medians, cannot yet be combined statistically using its meta-analysis program, Meta-view.

In contrast to some areas of clinical practice, such as cancer, heart disease, and prenatal medicine, the management of ESRD has not been characterised by large collaborative RCTs. The 47 relevant RCTs found were, therefore, as large a number as we had originally hoped for. Nevertheless, their value is limited. One reason is that they did not cover the six topics uniformly (see appendix 3, *Table 5*). Whereas 22 studies compared alternative haemodialysis membranes, none addressed what is arguably the most important question, the comparison of haemodialysis with CAPD (topic 6). Another reason for their limited value is that the 47 trials were of variable but generally poor quality. Many were poorly reported making it difficult to judge the methods used. Details of attempts to avoid bias, such as methods of randomisation or analyses, were often not available. When it was possible to judge, the methods were often sub-optimal. Drop-outs were common following changes in clinical management and yet intention-to-treat analyses were the exception rather than the rule. Also, the issue of appropriate censoring of data after transplantation was often not considered.

Most trials included small numbers of participants, so that estimates of effects were often imprecise, particularly for dichotomous variables. Even after combining data, where possible, from more than one trial, the CIs for these estimates were often so wide that it was frequently not possible to rule out a clinically important difference, even when the point estimate suggested that there was none. (To put this another way, lack of statistical significance could not be taken as 'no clinically significant difference' in many comparisons.)

Another concern when reviewing small trials such as those included in these reviews is the possibility that selective publication of the results of small trials which showed 'statistically significant differences', combined with the failure to report less promising results of other small trials, may lead to important publication bias. Contact with the authors of the included RCTs and with manufacturers did not uncover unpublished RCTs. This may mean that these data do not exist or that contacts were unwilling to release details or were not aware of the importance of unpublished results to the systematic review process. For the majority of outcomes, there were too few trials to explore the impact of publication bias formally, for example, using a funnel plot. For a small number of outcomes, however, the construction of a funnel plot was possible. For example, within the comparison of bicarbonate with acetate dialysate, funnel plots could be constructed for the outcomes of patients experiencing headaches and nausea/vomiting. These are presented in *Figures 4* and *5*. A publication bias effect is suggested because

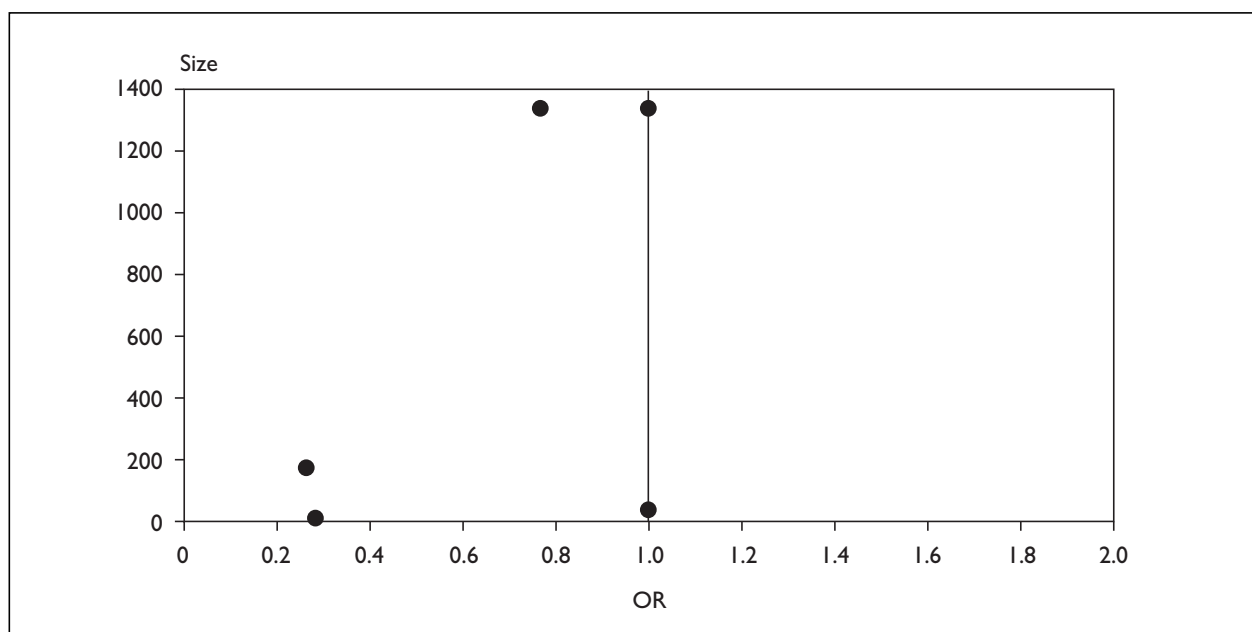


FIGURE 4 Funnel plot for bicarbonate versus acetate dialysate – patients experiencing headaches

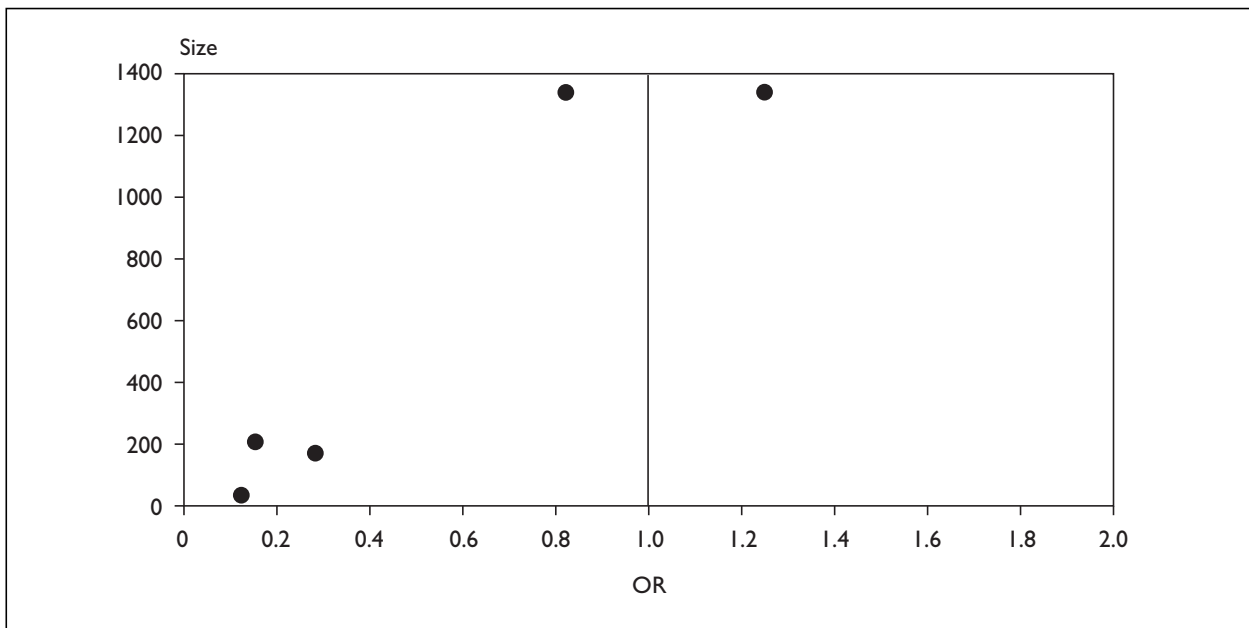


FIGURE 5 Funnel plot for bicarbonate versus acetate dialysate – patients experiencing nausea/vomiting

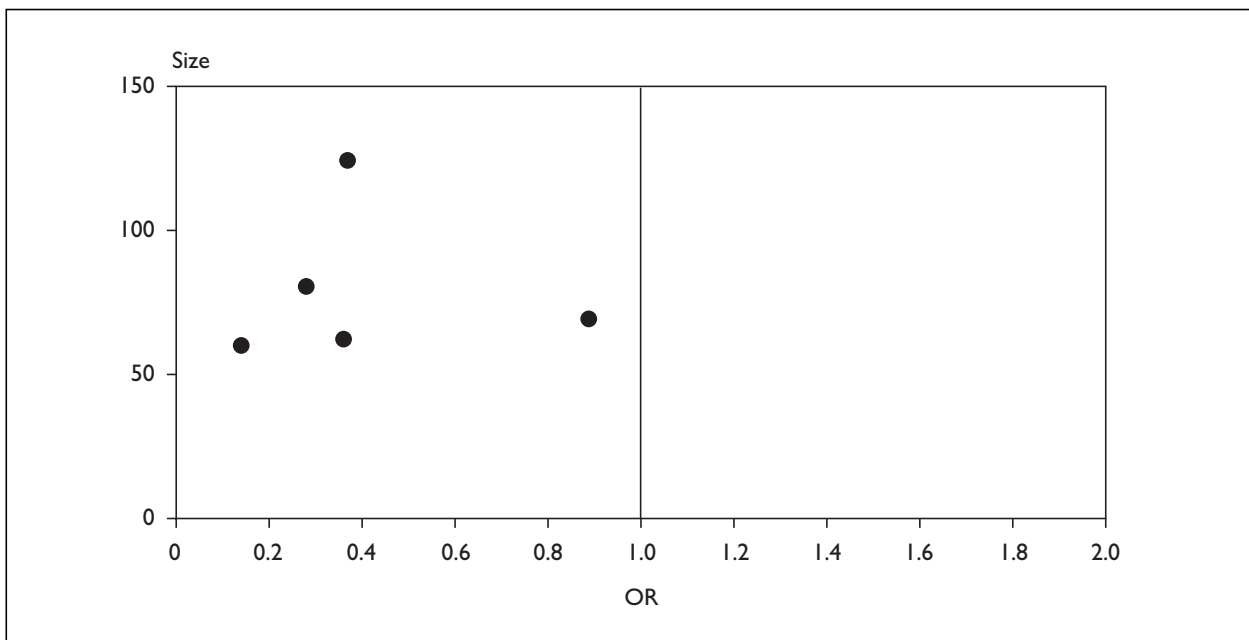


FIGURE 6 Funnel plot for Y-set versus standard spike delivery system – patients experiencing peritonitis

there are no small trials reporting in favour of the control treatment. The interpretation of the results of small trials for the comparison of bicarbonate versus acetate dialysate should, therefore, be treated with caution. A similar effect is seen in the funnel plot for peritonitis episodes for the comparison of Y-set versus standard spike delivery systems in CAPD (*Figure 6*). For the comparison of synthetic versus cellulose membranes for symptomatic/ treatment requiring hypotension, however, there was no evidence to suggest publication bias, with comparable representation of both

positive and negative results among the small trials (*Figure 7*).

A related concern is selective reporting within the 47 RCTs of outcome data that are statistically significant. It is not reassuring in this respect that data are available from only a minority of relevant trials for many comparisons in the reviews.

The generalisability of the trials is also limited. Their eligibility criteria were usually restrictive (aiming to study a tightly defined group of patients)

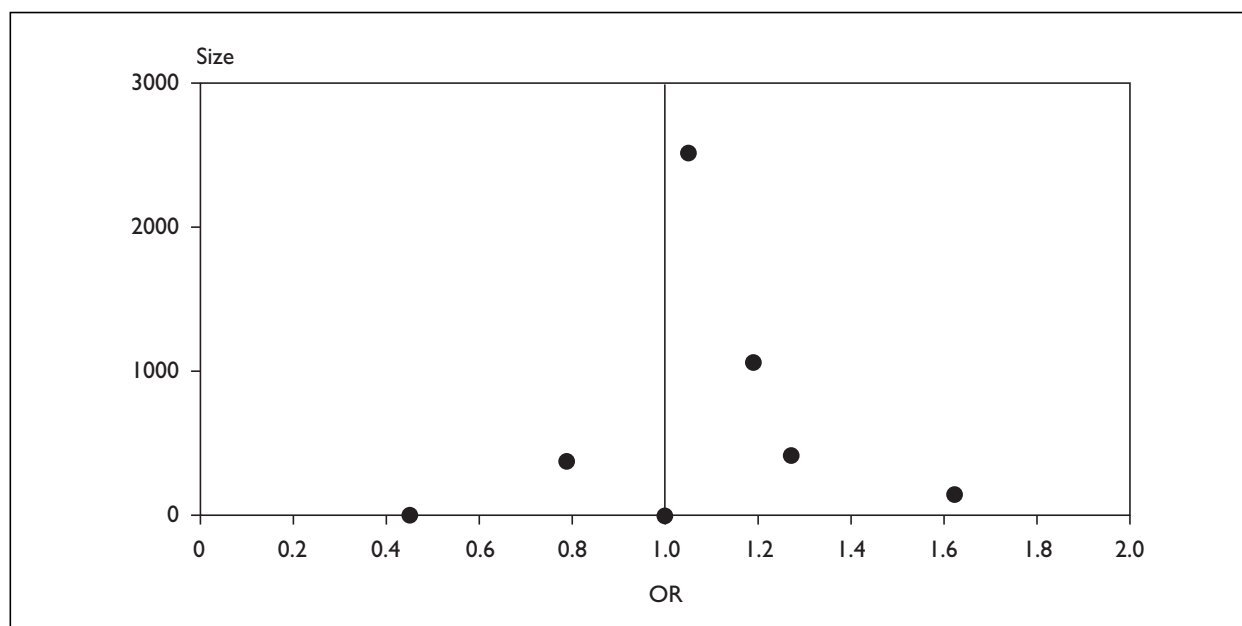


FIGURE 7 Funnel plot for synthetic versus cellulose membranes – patients experiencing symptomatic or treatment-requiring hypotension

and they were mostly conducted at single centres. They also tended to concentrate on short-term surrogate measures of outcome, such as biochemical measures of dialysis adequacy, rather than parameters directly relevant to patients, such as quality of life, treatment complications and survival. This latter consideration applied, in particular, to crossover design trials. In a chronic condition such as ESRD, randomised crossover designs appear attractive but their value is limited because they cannot be used to assess the longer-term consequences of alternative approaches to care.

The style of the trials was therefore explanatory rather than pragmatic. They tended to test specific hypotheses about efficacy, rather than compare the effectiveness of alternative policies for dialysis, which incorporate changes in management when clinically indicated. Whereas explanatory trials are useful for exploring new developments in dialysis in an ‘ideal’ setting, they are of limited value for assessing alternative approaches to dialysis that might be used within the NHS in terms of outcomes, including costs, that are most important to patients, providers and purchasers. Pragmatic designs are needed for this.

An important point to consider in an economic evaluation is that costs are subject to economies of scale. Generally speaking, the more units of a product that are purchased the cheaper the unit price becomes. In the economics analyses contained in this report, this has been taken into account by using, where possible, average selling prices which tend to be less than manufacturers’ quoted ‘list’ prices. However, this provides only

an indication of possible economies of scale. For any local situation, information on resource use contained in each of the economic evaluations can be combined with local data on prices. One can then judge whether the local costs are worth the benefits that they provide.

Reflecting our wish to inform patient care within the NHS, the systematic reviews have incorporated economic evaluations. Although it is important to determine which interventions are most effective, it is increasingly widely recognised that this must be balanced against the relative costs and cost consequences of alternative interventions. An economic evaluation relates cost to effectiveness. The RCTs appropriate to our topics, although providing some information on effectiveness, were found not to provide adequate costing data to allow a full evaluation to be made. In our economic evaluations, data from the reviews of randomised trials were used, where possible, to estimate resource use associated with the initial interventions and differential rates of measures of effectiveness with resource consequences (expressed as adverse events, such as complications). When such data were not available, use was made of cost data from the less methodologically rigorous studies identified by our separate ‘economics literature search’.

These studies were also used to obtain estimates of the magnitude of resources used in each option evaluated (unless more accurate data could be obtained from UK-based costings). Reflecting the lack of pragmatic trials of different starting therapies, neither long-term cost data nor

long-term estimates of probabilities of switching between modes of treatment were available.

The results of the economic evaluations have been constructed around a 'standard' patient. It is possible that there are definable subgroups of patients for whom the costs and benefits may vary substantially from the standard. Although this is a recognised issue in economic terms⁸ there are insufficient data available to perform reliable subgroup analyses. The framework developed and the information presented currently provide, therefore, the best available evidence on which to base judgements about treatments in definable subgroups.

In certain of the economic evaluations, the analysis is constrained because the 'lifetime' costs of treatment have not been identified. The economic evaluation of alternative forms of CAPD delivery systems was the principal evaluation where this type of cost data would have been useful. Unfortunately, the necessary data on, for example, the probabilities of patients dying or switching modalities were not available, and it was considered that this information could not be abstracted in a sufficiently robust form from a non-randomised study to make extending the analysis in this way worthwhile. However, when reliable data were obtainable and the type of analysis was appropriate, for example, for the comparison of CAPD and CCPD, patient lifetime costs were calculated.

For all the reasons outlined above, the value of this work is limited by the material available to us from relevant previous primary research. Nevertheless, the reviews do provide clear guidance for patients, providers and purchasers on some of the six key decisions:

- choice of dialysate for haemodialysis
- duration of haemodialysis
- choice of catheter in CAPD

and provide a basis for an informed decision where a judgement has to be made between possible greater effectiveness and greater cost:

- choice of membrane for haemodialysis
- use of CCPD.

They also demonstrate to those who commission and perform research where further research is needed:

- choice of membrane for haemodialysis
- duration of haemodialysis

- further evaluation of CCPD
- choice between haemodialysis and CAPD as the initial modality for patients starting dialysis.

As indicated earlier, information about effectiveness and efficiency is necessary but not sufficient when making decisions about health care. We have already alluded to the changing health needs of the population served by the NHS and the particular requirements and preferences of some of the patients with ESRD. Data from renal registries describing those currently receiving long-term dialysis and their management will clarify the applicability of our findings and the potential for change. For example, bicarbonate as a buffer in haemodialysis is already used in most renal units.

There may be criticisms that much time and effort has been used in some of these reviews to confirm what clinicians have felt about some aspects of treatment for some time; again, the use of bicarbonate is an example. A formal systematic review, however, can give that argument conviction, set it in the context of cost and prevent further expensive unnecessary studies being carried out. When the review began, scarcely any similar work had been carried out in the subject area of renal disease, particularly ESRD. Our group was truly multidisciplinary including nephrologists, health services researchers, health economists and librarians and information officers. The whole group met weekly and we consider that this successful integration of the various types of expertise and skills is manifest in this report.

Despite the involvement of experienced health service researchers, nephrologists and health economists, it took time to define the best search strategy and we were surprised that our search yielded as many as 12,000 abstracts. This sort of exercise will, however, be significantly easier in the future. The Cochrane Collaboration will be performing broad searches of all the principal electronic databases for all RCTs, irrespective of subject area. Possible RCTs identified in this way will contribute to a new register (CENTRAL) within the Cochrane Library and so, in the future, it will only be necessary for groups of researchers to search the CENTRAL register for trials relevant to a particular subject area. We do plan to disseminate our findings actively. The reviews are likely to have the greatest influence on professional groups.

Nephrologists have The Renal Association as a platform for dissemination and discussion, and the Department of Health and its equivalents

at the Scottish and Northern Ireland Offices also have wide-ranging information dissemination systems.

The Renal Association (in conjunction with the Royal College of Physicians of London) has produced a document, *Treatment of adult patients with renal failure – recommended standards and outcome measures*.¹⁸ The results of systematic reviews such as this should, after discussion with all interested groups, inform these standards. Similarly, we hope that our findings will influence any later versions of the recently published *Review of renal services in England* by the Department of Health¹⁹ and appear in peer-reviewed journals. In this way the evidence gathered is more likely to be put into practice, and the process will be seen not as a threat but as an opportunity to provide optimum care for patients with ESRD.

This work is not seen as a ‘once-and-for-all’ exercise. The six reviews will be submitted for

publication in the Cochrane Database of Systematic Reviews, and regularly updated thereafter as new evidence becomes available. Also, the other RCTs that have been identified in the broad searches will be contributed to the Cochrane Collaboration, thus facilitating the systematic review of RCTs of other aspects of dialysis.

The project has highlighted the paucity of RCTs that usefully inform the key issues on the effectiveness and, hence, provision of NHS dialysis services for ESRD that were identified in the original commissioning brief. Ideally, the NHS needs evidence from large pragmatic trials comparing the management policies used in many renal units over a range of types of patient. This will require a culture shift away from the current explanatory style of research, investigating underlying mechanisms of dialysis in small groups of patients in single centres, to simply designed collaborative trials evaluating the longer-term impact of alternative dialysis policies on patients and the health service.



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Appendix I

Background information on ESRD and treatment

This appendix provides background information on renal failure and describes the services available for its treatment. It has been adapted from *Renal purchasing guidelines EL 96/35*, published by the NHS Executive in May 1996, and is reproduced with permission.

Renal disease

Diseases of the kidney are not as common as other important diseases such 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 7000 deaths per annum (Registrar General's figures) not including cancers of the kidney and associated organs of the urinary tract such as bladder and prostate. However, around one-third of deaths of people with renal failure are not recorded as such in the death data, and in many cases – especially the elderly – there are associated illnesses which preclude the institution of RRT.

Over 100 different diseases affect the kidneys. These diseases may present early with features such as pain, blood or protein in the urine or peripheral oedema (swelling in the legs), or may remain undiagnosed until the patient recovers or the symptoms of renal failure develop. Much renal disease is self-limiting and often occurs and heals with few, if any, symptoms or sequelae.

Renal failure may be acute and reversible, which occurs in previously normal kidneys after major injury such as crush injuries or major surgery, in the presence of overwhelming infection, or if the blood supply to the kidneys is compromised by failure of the heart's pumping action, or losses of blood, salt or water so that the blood pressure drops and the kidneys are no longer supplied with blood. In this case, renal support is needed only for days or weeks before renal function returns. However, about half such patients die during the illness because of other conditions.

More common is chronic irreversible renal failure in which the kidneys are slowly destroyed over months or years. Chronic irreversible renal failure slowly erodes kidney function. To begin with there is little to see or find, and many patients present for medical help late in their disease, or even in the terminal stages. Tiredness, anaemia, a feeling of being 'run down' are often the only symptoms, plus headache, breathlessness and perhaps angina if high blood pressure is present – as happens often as the kidneys fail, or as the prime cause of the renal disease (ESRD). Ankle swelling may occur if the loss of protein in the urine is particularly great.

The stages of chronic irreversible renal failure are often given different terms: chronic renal insufficiency for the early stages, chronic renal failure when it has become obvious, and end-stage renal failure when it reaches its terminal stages. At this point if nothing is done the patient will die.

Two forms of treatment are available, however, which are complementary to each other and may both be needed if end-stage renal failure is to be treated – dialysis and renal transplantation.

Ethnicity and age are considered to be the key socio-demographic determinants of ESRD. There is cogent evidence that the incidence of ESRD increases significantly with age. While not achieving European levels, the trend in the UK has been for older patients to be accepted, resulting in the rising age-profile of new patients in recent years. Evidence from the USA suggests that the relative risk of ESRD in the black population (predominantly of African origin) is two to four times higher than for whites.¹ Data collected during the Review of Renal Specialist Services in London suggest that there is a similar increased risk of renal failure in the ethnic populations (Asian and Afro-Caribbean) in the Thames Regions compared with whites.² People from both of these groups have a higher prevalence of non-insulin-dependent diabetes and patients in these groups with diabetes are more likely to develop renal failure than whites. This partly explains the higher acceptance rate of Asians on to RRT programmes.

Categories of renal disease

Most renal diseases that cause renal failure fall into a few categories, including the following.

Autoimmune disease

'Glomerulonephritis' describes a group of diseases in which the glomeruli (the filters which 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; however, treatment makes only a small impact on the progress of this group of patients into ESRD.

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). In some patients, progressive kidney damage begins after some years of diabetes, particularly if blood sugar and high blood pressure have been poorly controlled. This is a particularly common and severe problem in patients from the Indian subcontinent. Careful lifelong supervision has a major impact in preventing kidney damage.

High blood pressure

Severe (accelerated) hypertension damages the kidneys but the damage can be prevented, and to some extent reversed, by early detection and early treatment of high blood pressure. In patients of Afro-Caribbean origin, hypertension is frequently the only presumptive causative factor of renal failure. The relationship between high blood pressure and the kidney is being studied to see to what extent treatment to bring blood pressure to normal levels might reduce the incidence of ESRD in such target groups. It is possible that other factors are also involved.

Obstruction

Anything which obstructs the free flow of urine can cause back-pressure 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, benign prostatic hyperplasia (BPH) is so common that it becomes a major cause of renal failure over the age of 70 years.

Infection of the urine

Cystitis is a very common condition affecting about half of all women at some time in their life and

rarely has serious consequences. Infection of the urine in young children or patients with obstruction and other abnormalities of the urinary tract or kidney stones may result in scarring of the kidney and eventual kidney failure.

Genetic disease

One common disease – polycystic kidney disease (PKD) – and many rare inherited diseases affecting the kidneys account for about 8% of all kidney failure in Britain. Although present from birth, PKD 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.

Prevention of renal failure

Prevention of chronic irreversible renal failure is not often possible, but better control of diabetes and high blood pressure and relief of obstruction have much to offer, provided that the condition can be recognised early in the course of the disease, before much renal damage has occurred.

Screening for renal diseases has not been practised, because of the relatively low incidence of cases. 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 of renal failure can be identified.

The earliest possible assessment of patients likely to need RRT provides the greatest cost-effectiveness. This is reinforced by the growing awareness that medical and other complications frequently arise caused by factors which could have been detected and modified if there had been time for assessment. The surveillance of at-risk groups in general practice might assist by bringing patients who will require RRT to the attention of nephrologists as early as possible. Hospital doctors in all specialities should be aware that mild renal failure requires prompt assessment by a nephrologist.

Renal failure is often accompanied by other disease processes. Some of these are due to the primary disease; for example, diabetes causes renal failure, 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 cardiovascular diseases, peripheral vascular disease, chronic bronchitis and arthritis are particularly common in older patients with renal failure. All these

conditions (called collectively 'co-morbidity') can influence the choice of treatment for renal failure and may reduce its benefits. Expert assessment of the patient before ESRD can reduce co-morbidity and increase the benefit and cost-effectiveness of treatment. Thus early detection and referral of patients at risk of renal failure is important. Evidence from the USA 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.³ Studies of patients in the UK confirm this.

Renal replacement therapy

The term RRT is used to describe those treatments for ESRD where, in the absence of kidney function, the removal of waste product from the body is achieved by dialysis and other kidney functions are supplemented by drugs. It is also the term which covers the complete replacement of all kidney functions by transplantation. Patients with ESRD usually change treatment modalities during their time on RRT. They may begin with one form of dialysis, change to another and then receive a transplant; if the transplant fails they return again to dialysis. The modalities of treatment can therefore be seen as complementary.

Dialysis

Dialysis involves the cleansing or washing of the blood by the use of fluids which allow the toxic substances to leave the body by a route other than the kidneys; in addition it is possible to regulate the composition of the body fluids and the amount of water and salts in the body by altering the composition of the fluids used, and by pressure or other forms of filtration.

The method used first 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 exchanged can take place. The disadvantage of this method is that some form of permanent access to the circulation must be produced which can be needled at every treatment. Each session lasts 4–6 hours and is needed three times a week.

The alternative is peritoneal dialysis, often carried out in the form of CAPD. In this technique, fluid is infused and withdrawn from the peritoneal cavity

which lies around the bowel; the washing fluid must be sterile, and peritonitis (infection and inflammation of the peritoneum) is a frequent complication. A silastic tube must be implanted into the peritoneum, and this may become kinked or malpositioned. The fluid is exchanged four times daily and hence remains in the abdominal cavity for about 4–5 hours during the day and for 8 hours overnight. More recently automated peritoneal dialysis has been introduced in which exchanges are carried out overnight by a machine and no exchanges are required during the day.

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

Renal transplantation

Renal transplantation replaces all the functions of the kidney, making EPO and vitamin D unnecessary. A single kidney is placed usually in the pelvis close to the bladder, and 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 other which can be used have many undesirable side-effects, including the acceleration of vascular disease so that myocardial infarcts and strokes are commoner in transplant patients than in age-matched controls. During subsequent years also, there is a steady loss of transplanted kidneys from a process of chronic rejection; treatment of this is unsatisfactory and many patients require a second or even third graft over several decades, and have to rely on dialysis in the meantime.

The main bar to expanding transplantation is the shortage of suitable kidneys to transplant. Although the situation could be improved, it is now clear that whatever social and medical structures are present or legislation is adopted, there will be inevitably be a significant 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. Experiments using animal kidneys are under way but are still in the early stages. It will be some time before we know whether xenotransplantation, as this

procedure is known, will contribute to the transplant programme.

The nature of renal services

The nature of the work in renal medicine is extremely varied. 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 a patient early for initial diagnosis and treatment. Inpatient work accounts for perhaps 5% of patients under care at any one time but is complex, and experienced medical advice must be available on a 24-hour basis. About 95% of renal work is sustained on an outpatient basis; this includes most RRT by dialysis and the care of transplant patients. There are four major components to renal medicine.

Renal replacement therapy

The most significant element of work is in relation to the preparation of patients in ESRD for RRT. Once accepted there is a requirement for medical supervision for the remainder of the patient's life. There is demographic evidence that the patient population will present increasing challenges for renal staffing as more elderly and diabetic patients are accepted for treatment.

Emergency work

The emergency work associated with the specialist consists of the following.

- The treatment of acute renal failure, often involving multi-organ failure, and acute-on-chronic renal failure. Close cooperation with other medical specialities including intensive care is therefore a vital component of this aspect of the service.
- There is a significant workload of medical emergencies arising from an ESRD programme which is bound to increase in proportion to the demands on the main programme.

Routine nephrology

There is a significant workload associated with the immunological and metabolic nature of renal disease which requires investigative procedures in an inpatient setting.

Investigation and management of fluid and electrolyte disorders

This is variable proportion of the nephrologist's work, depending on the other expertise available in the hospital.

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.

Acute uraemic emergencies

Up to 40% of patients requiring RRT present at the time when dialysis is needed; this constitutes an acute uraemic emergency, since only immediate therapy will save life. Any such patient should receive appropriate assessment and treatment, and renal units must have the facilities to deal with them. However, other patients with potentially reversible renal failure who present in this way eventually recover renal function and do not require long-term RRT. It is impossible to distinguish immediately between cases in which recovery will occur and those in which it will not, and clinicians need time to assess this. Even if renal function cannot be recovered, there may be other reasons for not proceeding to long-term RRT, and time is required for this to be determined.

Research

Renal disease has become a defined sub-speciality only within the last 30 years but the kidney has stimulated academic interest for much longer due to its central role on metabolism, hypertension and immunological disease. The MRC, Wellcome Trust and the National Kidney Research Fund spend annually over £3 million in departments with an interest in renal medicine, renal physiology and transplantation.

References

1. US renal disease survey annual report 1993. Washington DC: Department of Health, Education and Welfare, 1993.
2. Report of the review of London's renal services. London: HMSO, 1993.
3. Byrne C, Vernon P, Cohen J. Chronic dialysis in older patients. *JAMA* 1994;**271**(1).

Appendix 2

Literature search strategies

General search strategies used in main electronic databases

The following general search strategies for the identification of RCTs or quasi-RCTs in the management of ESRD were used.

Medline

Medline (National Library of Medicine, electronic version of *Index Medicus*, USA) on OVID, CD plus, was searched from 1966 to June 1996 using the following strategy.^a

- 001 renal replacement therapy/
- 002 exp hemodialysis/
- 003 exp hemofiltration/
- 004 kidney, artificial/
- 005 exp peritoneal dialysis/
- 006 ultrafiltration/
- 007 dialysis/
- 008 kidney failure, chronic/
- 009 kidney failure, acute/
- 010 uremia/
- 011 (hemodia\$ or haemodia\$ or hemofilt\$ or haemofiltrat\$ or diafilt\$).tw.
- 012 (ultrafilt\$ or dialy\$ or biofilt\$).tw.
- 013 ((kidney\$ or renal) adj2 (replac\$ or artificial or extracorporeal)).tw.
- 014 ((kidney\$ or renal) adj2 (disease\$ or failure\$ or sufficien\$ or insufficien\$)).tw.
- 015 esrd.tw.
- 016 ur?emi\$.tw.
- 017 or/1-16
- 018 controlled clinical trial.pt.
- 019 randomised controlled trial.pt.
- 020 randomised controlled trials/
- 021 random allocation/
- 022 double blind method/
- 023 single blind method/
- 024 clinical trial.pt.
- 025 exp clinical trials/
- 026 (clin\$ adj4 trial\$).tw.
- 027 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj4 (blind\$ or mask\$)).tw.
- 028 placebo\$

- 029 placebo\$.tw.
- 030 random\$.tw.
- 031 research design/
- 032 volunteer\$.tw.
- 033 animal/
- 034 human/
- 035 33 not (33 and 34)
- 036 or/18-32
- 037 36 not 35
- 038 37 and 17

The search strategy 018-037 is a translation from SilverPlatter syntax of the first two (plus the term volunteer\$) of the three stages of an optimised strategy recommended by the Cochrane Collaboration for the identification of RCTs (Dickersin, 1994).¹² Pilot searches combining the whole Cochrane strategy with the disease/intervention search terms resulted in too many irrelevant hits: to increase precision (specificity), but with the possible loss of some sensitivity, only the first two parts plus the term volunteer\$ were used.

Embase

Embase (Elsevier Science Publishers BV, electronic version of *Excerpta Medica*, Amsterdam) was searched from 1981 to June 1996 using the following strategy.^b

```
(( (controlled study)@KMAJOR,KMINOR,
(randomised controlled trial)@KMAJOR,
KMINOR, (clinical study)@KMAJOR,KMINOR,
(clinical trial)@KMAJOR,KMINOR, (major
clinical study)@KMAJOR,KMINOR, (prospective
study)@KMAJOR,KMINOR, (multicenter
study)@KMAJOR,KMINOR, (randomization)
@KMAJOR,KMINOR, (double blind procedure)
@KMAJOR,KMINOR, (single blind procedure)
@KMAJOR,KMINOR, (crossover procedure)
@KMAJOR,KMINOR, (placebo)@KMAJOR,
KMINOR) + ((kidney failure)@EX, (hemodialysis)
@EX, (hemofiltration)@EX, (artificialkidney)
@KMAJOR,KMINOR, (ultrafiltration)@KMAJOR,
KMINOR, (dialysis)@EX)) - ((nonhuman)
@KW - ((human)@KW + (nonhuman)@KW))
```

^a Key: / = MeSH term; exp = exploded MeSH term; \$ = wildcard; adj(n) = adjacent, within n words either side of the other term; ? = a letter may or may not be present; pt = publication type; tw = textword, searches in title and abstract.

^b Key: @KMAJOR,KMINOR = term present in either major or minor EMBASE keywords; comma ',' = Boolean operator 'or'; + = Boolean operator 'and'; @EX = exploded keyword search; minus sign '-' = Boolean operator 'not'.

Textword searching of Embase resulted in too many irrelevant hits. It was decided that, in view of time constraints, a more focused keyword search would optimise RCT identification.

Biosis

Biosis (Biological Abstracts Inc, electronic version of *Biological Abstracts*, USA) on SilverPlatter was searched from 1989 to June 1995 using the following strategy (searching in title, abstract and descriptor fields).^c

- #1: HEMODIA*
- #2: HAEMODIA*
- #3: HEMOFILT*
- #4: HAEMOFILT*
- #5: DIAFIL*
- #6: ULTRAFILT*
- #7: DIALY*
- #8: KIDNEY* near ARTIFICIAL
- #9: (KIDNEY* or RENAL) near (REPLAC* or ARTIFICIAL or EXTRACORPOREAL)
- #10: (RENAL or KIDNEY*) near (DISEASE* or FAILURE* or SUFFICIEN* or INSUFFICIEN*)
- #11: ESRD
- #12: UREMI* or URAEMI*
- #13: #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- #14: BC86215
- #15: CLIN* near TRIAL*
- #16: (SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*)
- #17: PLACEBO*
- #18: RANDOM*
- #19: VOLUNTEER*
- #20: #15 or #16 or #17 or #18 or #19
- #21: #13 and #14 and #20

CINAHL

CINAHL (CINAHL Information Systems, Cumulative Index of the Nursing and Allied Health Literature, USA) on OVID, CD plus, was searched from 1982 to March 1996 using the following strategy.^d

- 001 exp Clinical trials/
- 002 exp clinical research/
- 003 research/
- 004 random assignment/
- 005 research.pt.

- 006 (clin\$ adj25 trial\$.tw.
- 007 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).tw.
- 008 placebos/
- 009 placebo\$.tw.
- 010 random\$.tw.
- 011 exp Study Design (Non-CINAHL)/
- 012 volunteer\$.tw.
- 013 or/1-12
- 014 dialysis centers/
- 015 dialysis/
- 016 exp hemodialysis/
- 017 dialysis patients/
- 018 dialysis solutions/
- 019 Peritoneal Dialysis Therapy (Iowa NIC)/
- 020 renal osteodystrophy/
- 021 kidney artificial/
- 022 catheters dialysis/
- 023 nephrology nursing/
- 024 exp kidney failure acute/
- 025 kidney failure chronic/
- 026 exp uremia/
- 027 exp renal replacement therapy/
- 028 hemodia\$.tw.
- 029 haemodia\$.tw.
- 030 hemofilt\$.tw.
- 031 haemofilt\$.tw.
- 032 diafilt\$.tw.
- 033 ultrafilt\$.tw.
- 034 dialy\$.tw.
- 035 ((kidney\$ or renal) adj25 (replac\$ or artificial or extracorporeal)).tw.
- 036 ((renal or kidney\$) adj25 (disease\$ or failure\$ or sufficien\$ or insufficient\$)).tw.
- 037 esrd.tw.
- 038 ur?emi\$.tw.
- 039 or/14-38
- 040 13 and 39

Cochrane Library

The following databases, available through the Cochrane Library (Cochrane Collaboration, Oxford: update software, April 1996; Issue 1, on CD-ROM: available from BMJ Publishing Group, London) were systematically searched.

- The Cochrane database of systematic reviews
- Database of abstracts of reviews of effectiveness (DARE)
- The Cochrane controlled trials register.

^c Key: * = wildcard; near = in the same sentence; BC86215 = human.

^d Key: / = MeSH term; exp = exploded MeSH term; \$ = wildcard; adj(n) = adjacent, within n words either side of the other term; ? = a letter may or may not be present; pt = publication type; tw = textword, searches in title and abstract.

The following search terms were used.^e

Renal replacement
Haemodia*
Hemodia*
Dial*
CAPD
Peritoneal dialysis
Artificial kidney
Renal failure
Kidney failure
Uraemia
Uremia
CRF
End-stage renal disease
End-stage renal failure
ESRD
ESRF

The search strategy used was a modified version of the search strategy used with Medline (OVID) (01–17) as outlined above. No methodology search terms were used. The first version of the Cochrane Library was used for this search and, because of difficulties experienced using multiple search terms and saving search strategies, each of the search terms had to be individually entered. The search was performed with a nephrologist assessing the trials identified on screen, printing out only those hits relevant to the six review topics.

Search strategies in other databases

Specific strategies were developed for searching the following specialist databases.

Chemabs (Chemical Abstracts Service, Columbus, Ohio, USA; electronic version of *Chemical Abstracts*) on STN. Years searched: 1967–1 July 1995 (for acetate versus bicarbonate only).

The following three sets of search terms were used, combined with the Boolean operator AND:^f

- renal terms – hemodia*, haemodia*, hemofiltrat*, haemofiltrat*, dialy*, (kidney# or renal) (2A) (artificial or replac^g or extracorporeal)

- buffer terms – 144-55-8 or bicarbonate or carbonic(w)acid(w)monosodium(w)salt, acetate or 127-09-3, acid(w)base(w) (imbalance# or balanc# or equilibri?) or acidosis, buffer?
- RCT terms – control?(2A)clinical(w)trial? or random?, (singl# or doubl# or trebl# or tripl#) (A) (blind? or mask?), placebo#.

SIGLE (System for Information on Grey Literature in Europe, compiled by EAGLE) on SilverPlatter. Years searched: 1980–June 1996. Search term: renal.

CRIB (Current Research in Britain, 10th edition, 1995. Book format, published by Cartermill Publications, London). Search term: nephrology.

NRR (National Research Register, NHS Executive; 14th consolidation, September 1996) (version prepared by NHS Executive, Anglia and Oxford). It includes all 6678 records in the 14th consolidation (on Idealist).

Textword search^g of all fields: renal, haemodialy*, haemofilt*, dialy*, kidney*

Economic search strategies

The following supplementary searches were performed for studies relevant to the economic evaluation.

Medline economics search terms

Medline was searched from 1966 to August 1996 using the following strategy.^h

- MeSH terms – workload, health resources, length of stay, hospitalization, explode costs and cost analysis, economics
- terms in title or abstract – cost\$, economic\$, resource\$, efficien\$ (limited to economics subheading), marginal analy\$, utility, QALY, quality adjusted life year\$, HYE, healthy years equivalent\$, estimat\$ adj2 (benefit or harm\$).

These terms were combined using the Boolean operator OR and then combined with line 17 (see general Medline strategy above) using the Boolean operator AND.

^e Key: * = wildcard.

^f Key: * = wildcard; # = one or zero characters; (n)A = adjacent, in any order, within n words either side of other term; ? = truncation, any number of characters; w = adjacent, in same order, to other term.

^g Key: * = wildcard.

^h Key: / = MeSH term; exp = exploded MeSH term; \$ = wildcard; adj(n) = adjacent, within n words either side of the other term; ? = a letter may or may not be present; pt = publication type; tw = textword, searches in title and abstract.

Embase economics search terms

The database was searched from 1981 to August 1996 using the following strategy.ⁱ

- Terms in title, abstract or keywords – medical economics, health resource*, hospital care, hospitalization, cost, economic aspect, economic value of life, resource* allocation, resource management, efficiency, health care, quality of life.

These terms were combined using the Embase Boolean operator equivalent of OR (a comma) and then combined with the ESRD terms for use in Embase (see general Embase search strategy above) using the Embase Boolean operator equivalent of AND (+ sign).

Biosis economics search terms

The database was searched from 1989 to April 1996 using the following strategy (searching in title, abstract and descriptor fields).^j

- Terms in title, abstract or descriptor – economic*, workload, health resources, length of stay, hospitalization, hospitalisation, QALY, HYE, quality adjusted life year*, marginal analys*, cost*, resource*, utility, efficient*, estimat* near (benefit* or harm*).

These terms were combined using the Boolean operator OR and then combined with line 13 (see general Biosis search strategy above) using the Boolean operator AND.

CINAHL economics search terms

The database was searched from 1982 to March 1996 using the following strategy.

- CINAHL subject headings – economics, explode costs and cost analysis, hospitalization, health

resource allocation, economic value of life, productivity, explode quality of life.

These terms were combined using the Boolean operator OR and then combined with line 39 (see general CINAHL search strategy above) using the Boolean operator AND.

Other economics search terms

NHS economic evaluation database (NHS Centre for Reviews and Dissemination) – on-line. Date of search: 15 August 1996.^k

- Search terms – hemodia\$, haemodia\$, hemofilt\$, haemofilt\$, diafilt\$, ultrafilt\$, dialy\$, kidney\$, renal, ESRD, uraemia, uremia.

IBSS (British Library of Political and Economic Science) – on BIDS. Years searched: 1980–15 January 1997.^l

- Search terms – hemofilt*, haemofilt*, diafilt*, esrd, ultrafilt*, uremi*, uraemi*, hemodia*, haemodia*, ultrafilt*, kidney*, renal, dialy*.

Econlit (American Economics Association) – on SilverPlatter. Years searched: 1969–June 1996.^m

- Search terms – hemofilt*, haemofilt*, diafilt*, esrd, ultrafilt*, uremi*, uraemi*, hemodia*, haemodia*, ultrafilt*, kidney*, renal, dialy*, nephrologists.

The Economist (The Economist Newspaper Ltd, London) – on CD-ROM. Years searched: 1991–94.ⁿ

- Search terms – hemofilt*, haemofilt*, diafilt*, esrd, ultrafilt*, uremi*, uraemi*, hemodia*, haemodia*, ultrafilt*, kidney*, renal, dialy*.

ⁱ Key: * = wildcard.

^j Key: * = wildcard; near = in the same sentence.

^k Key: \$ = wildcard.

^l Key: * = wildcard.

^m Key: * = wildcard.

ⁿ Key: * = wildcard.

Appendix 3

Results of literature searches

Introduction

Over 16,000 abstracts of published articles were considered for inclusion in both the reviews of effectiveness and the economic evaluation. In this appendix the authors describe:

- how they were first identified
- how many were judged to be possible RCTs relevant to RCTs relevant to ESRD
- how many of these were concerned with the six specific topics chosen for review
- how many were confirmed as RCTs suitable for inclusion
- how many were considered in the economic analyses.

Since no previous work whatsoever has been undertaken in the area of ESRD, it was considered that a broad search was appropriate and would be useful for the Cochrane Renal Review Group's register of trials.

Results of searches for RCTs for assessing effectiveness

The number of abstracts of possibly relevant studies generated by the systematic searches of the five

electronic databases are shown in *Figure 8*. In total, of nearly 12,000 abstracts assessed, 2085 were thought to be possible RCTs or quasi-RCTs and, of these, 340 were later judged on review of the full report to be RCTs or quasi-RCTs related to the management of ESRD. A total of 39 were relevant to one or more of the six topics. The dividend from each of the five databases is shown in *Table 4*. Of the 39 RCTs found, 34 (87%) were identified on Medline. The next largest number came from Embase but the dividend expressed as a proportion of abstracts identified was low (about 1/1000).

The number of trials relevant to individual reviews varied (*Table 5*). The largest number were comparisons of haemodialysis membranes. No RCTs were found for what is arguably the most important review, the comparison of haemodialysis with CAPD.

The sources of the eight additional RCTs included in the reviews are summarised in *Table 6*.

Although trials related to the management of ESRD were found in other databases and during hand-searching of *Kidney International*, none of these were included in any of the six reviews as they did not fit the eligibility criteria. All eight

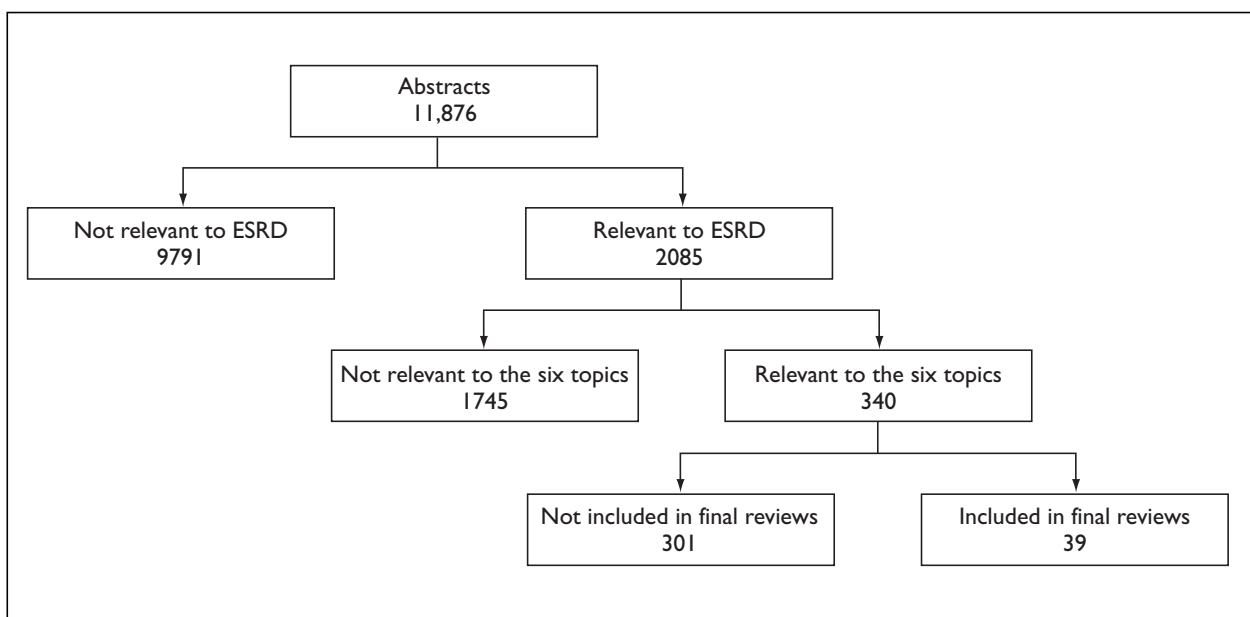


FIGURE 8 Number of possible RCTs or quasi-RCTs as screening process progresses (electronic searches only)

TABLE 4 Number of studies identified at each stage of the systematic electronic search according to database search

Source	Number of studies identified by electronic searches (includes duplication)	Number of possible RCTs/quasi-RCTs relevant to ESRD identified by reading retrieved citations/abstracts	Number of possible RCTs or quasi-RCTs relevant to six selected topics	Number of RCTs included in final review
Medline	5429	1480	243	34
Embase	4764	391	81	4
CINAHL	366	25	10	0
Biosis	1317	189	4	1
Cochrane Library	N/A ¹	N/A ¹	2	0
TOTAL	11,876	2085	340	39

¹ A nephrologist searched this database on screen and selected RCTs/CCTs relevant only to the six topics. For search strategy see appendix 2

TABLE 5 Number of potential RCTs or quasi-RCTs identified from the systematic electronic search for each selected topic at each stage of the assessment process

Topic	Number of possible RCTs/quasi RCTs after abstract assessment	Number of RCTs included in final review
Haemodialysis membranes	145	20
Acetate vs. bicarbonate	85	12
Haemodialysis duration	39	1
CAPD catheters	53	5
CCPD vs. CAPD	13	1
CAPD vs. haemodialysis	33	0
TOTAL	368¹	39

¹ Some studies cover more than one topic

additional RCTs were found from searching the reference lists of known RCTs or were made known to the authors by experts in this field.

The results of the handsearching of *Kidney International* from 1988 to 1995 inclusive are shown in Table 7. Of a total of 223 possible RCTs or CCTs, 107 were relevant to ESRD, 68 were not identified in the electronic searches and 33 were thought to

be relevant to one or more of the six topics. However, none of these were RCTs which reported data relevant to any of the predetermined outcome measures and therefore none of these studies were included in the reviews.

The results of the handsearching of the conference proceedings in *Kidney International* for the year 1994 are presented in Table 8. Although 15 possible RCTs were relevant to the six topics, none were included in the final reviews. However, the handsearching will contribute to the international Cochrane Collaboration work and help identify all RCTs and quasi-RCTs. Of the articles in Medline, 129 were incorrectly tagged and will be re-tagged by the National Library of Medicine (USA) as RCTs or CCTs. In addition, the 64 RCTs and CCTs identified in the conference proceedings, which are not normally indexed in Medline, will be included on a new auxiliary Medline database currently under development.

Table 9 is a summary of where the 47 RCTs included in the reviews were identified; 34 (72%) were identified from Medline.

Most of the studies identified in the supplementary economics searches were found in Medline and Embase (Table 10). In contrast to the findings for RCTs, the largest number were relevant to the comparison of haemodialysis and CAPD (Table 11).

TABLE 6 Numbers of possible RCTs from sources other than systematic searches of electronic databases

Source	Number of studies identified ¹	Number of possible RCTs relevant to ESRD ²	Number of possible RCTs relevant to topics ^{2,3}	Number of RCTs included in final review
Other databases ⁴	269	122	9	0
Hand-searching	287	133	48	0
Reference lists and experts in the field	56 ⁵	N/A ⁶	140	8
Subtotal (all other sources)	612	255	197	8

¹ Some reports were identified from more than one source
² Included controlled trials with quasi-random methods of allocation
³ Relevant to the six selected topics
⁴ Chemabs, SIGLE, CRIB and NRR
⁵ Number of reference lists checked
⁶ Collected possible RCTs for the six topics only

TABLE 7 Results of hand-searching Kidney International (excluding conference proceedings)

Year searched (vol)	Number of articles	CCTs ¹	RCTs ²	Total number of RCTs and CCTs	Number of RCTs and CCTs relevant to ESRD	Number of RCTs and CCTs not identified in electronic search	Number of RCTs and CCTs relevant to the six topics not identified in electronic search	Number to be amended in Medline because possible RCT or CCT	Number of RCTs included in final reviews
1995 (47, 48) ³	466	7	15 + 2 meta-analysis	22	7	4	1	12	0
1994 (45, 46)	533	15	27	42	14	4	3	17	0
1993 (43, 44)	477	9	19	28	15	14	9	19	0
1992 (42, 41)	432	13	21	34	19	10	1	18	0
1991 (40, 39)	369	8	7	15	9	3	3	9	0
1990 (38, 37) ³	311	10	11	21	16	8	7	14	0
1989 (36, 35)	335	8	21	29	6	4	1	12	0
1988 (33, 34)	310	26	6	32	21	21	8	28	0
Total	3233	96	127	223	107	68	33	129	0

¹ CCT. If an eligible trial has not been explicitly described as 'randomised', CCT is used as a collective term to distinguish possible RCTs and quasi-RCTs from 'definite' RCTs. Possible RCTs include trials that do not state the method of allocation but have treatment and control groups derived from a single group of participants. Examples of quasi-random processes for assigning treatments are coin flips, odd-even numbers, patients' social security numbers, days of the week, and patient record numbers. This conforms with the National Library of Medicine (USA) definition of an RCT.

² RCT. If the trial meets the four eligibility criteria (given below) and the author(s) state explicitly (usually by using some variant of the term 'random' to describe the allocation procedure used) that the groups compared in the study were established by random allocation. This conforms with the National Library of Medicine (USA) definition of an RCT. Eligibility criteria: the study compares treatment in human beings; the study is prospective in nature, i.e. the interventions are planned prior to the experiment taking place, and exposure to each intervention is under the control of the study investigators; two or more treatments or interventions are compared with one another (one may be a no-treatment control group); and the most important aspect is that assignment to a particular intervention is intended to be random, i.e. not deliberately selected in any way. Units of randomisation may be individuals, groups (communities, schools, or hospitals), organs or other parts of the body (such as teeth).

³ The years used to obtain the 'gold standard'.

(Footnotes 1 and 2 are based on material taken, with permission, from the Cochrane Handbook (1997), (Mulrow CD, Oxman AD (editors) – see reference 9, main report).

TABLE 8 Results of hand-searching conference proceedings for 1994 in Kidney International

<i>Kidney Int</i>	Organisation	Number of abstracts	CCTs	RCTs	Total number of CCTs & RCTs ¹	Number of RCTs & CCTs relevant to ESRD	Number of RCTs & CCTs relevant to the six topics	Number of RCTs included in final review
vol 45	Portuguese Society of Nephrology	48	2	1	3	3	1	0
	Australian & New Zealand Society of Nephrology	112	2	4	6	2	0	0
	Swiss Society of Nephrology	46	3	1	4	4	2	0
vol 46	Spanish Society of Nephrology	152	19	4	23	9	6	0
	Australia & New Zealand Society of Nephrology	97	5	5	10	3	3	0
	Société de Nephrologie	24	1	1	2	1	1	0
	Dutch Society of Nephrology	50	7	2	9	2	1	0
	Brazilian Society of Nephrology	75	5	2	7	2	1	0
Total		604	44	20	64	26	15	0

¹ Conference proceedings are not indexed on Medline. National Library of Medicine (USA) plans to have an auxiliary database which will include proceedings and journals not normally indexed on Medline

TABLE 9 All sources of RCTs included in the six reviews

	Number of included RCTs	Medline	Embase	CINAHL	Biosis	Cochrane Library	Authors & other experts	Reference lists	Hand-searching
Haemodialysis membranes	22	16	3	0	1	0	2 ¹	0	0
Acetate vs. bicarbonate	18 ²	12	0	0	0	0	1 ³	5	0
Haemodialysis duration	1	1	0	0	0	0	0	0	0
CAPD catheters	5 ⁴	5	0	0	0	0	0	0	0
CCPD vs. CAPD	1	0	1	0	0	0	0	0	0
CAPD vs. haemodialysis	0	0	0	0	0	0	0	0	0
TOTAL	47	34	4	0	1	0	3	5	0

¹ Found by two of the authors of this report during the course of their personal literature update
² More than one relevant RCT appeared in some of the published reports
³ Kindly given by a colleague
⁴ Six RCTs altogether but two reports were of the same trial, therefore counted as five included RCTs

TABLE 10 Systematic electronic search for studies covering the economic aspects of the six topics by source

Source	Number of studies identified by electronic searches	Number of possible studies relevant to the economic aspects of the six topics
Medline	2225	467
Embase	1849	338
Biosis	3	0
Econlit	21	7
IBSS	18	0
CINAHL	30	7
Other: The Economist	16	0
NHS Economic Evaluations Database	6	1
Total	4168	820

TABLE 11 Numbers of studies, organised by topic, from the systematic electronic search covering the economic aspects of the six topics

Topic	Number of studies potentially relevant to the economic aspects of each of the six topics
Haemodialysis membranes	85
Acetate vs. bicarbonate dialysate	41
Haemodialysis duration	109
CAPD catheters	34
CCPD vs. CAPD	22
CAPD vs. haemodialysis	529
Total	820

Appendix 4

Systematic review I: Comparison of synthetic with cellulose and modified cellulose membranes in the haemodialysis of patients with ESRD

Background

When the kidney fails, the blood-borne metabolites of protein breakdown and water cannot be excreted. The principle of haemodialysis is that such substances can be removed when blood is passed over a semi-permeable membrane with dialysate flowing on the other side. Metabolites are removed mainly by diffusion and water by applying a pressure gradient across the membrane.

Cellulose-based membranes are produced principally from cotton. They were the first membranes produced for dialysis and in their standard form have a low hydraulic permeability ($< 10 \text{ ml/h/m}^2/\text{mmHg}$) and are commonly known as low-flux membranes. They characteristically also have poor clearance of molecules larger in size than urea and creatinine, which may be responsible for some of the clinical features of uraemia. In recent years, standard cellulose membranes have been modified to make both larger molecule and water removal more efficient; such membranes are called modified cellulose, substituted cellulose or semi-synthetic membranes and can more readily be made to have a higher flux than cellulose membranes. They are generally more expensive than standard membranes.

In the early 1970s, synthetic polymer-based membranes became available which could be manufactured to have either high- or low-flux characteristics. They may remove β_2 microglobulin, a middle molecule which may cause dialysis-related amyloid disease, more effectively, particularly those which have a high flux. Such membranes have been used by those wishing to reduce the number of hours in a dialysis session. Synthetic membranes are also regarded as more 'biocompatible', in that they incite less of an immune response than cellulose-based membranes. Dialysis membranes can be cleaned or 'reprocessed' after use and reused for the same patient. This practice is more common for the more expensive synthetic membranes.

The greater stimulation of the immune system by the cellulose membranes may increase patients' susceptibility to infection and malnutrition, and may also, through production of cytokines and stimulation of the complement system, be partially responsible for the adverse symptoms experienced during haemodialysis. It is of particular importance to evaluate the benefits of synthetic membranes, since they are generally about three to four times more expensive than cellulose or modified cellulose membranes. Despite the economic and practical importance of the choice of dialysis membrane, it is not clear to nephrologists or healthcare purchasers what the benefits of synthetic membranes are and, if benefits do exist, whether their extra cost can be justified.

Objectives

The objectives of this review are:

- to determine whether synthetic membranes offer clinically important advantages compared with standard or modified cellulose membranes in the haemodialysis of patients with ESRD
- to determine from the literature the resource-use implications of biocompatible membranes and to relate this to measures of effectiveness in an economic analysis.

Materials and methods

Criteria for considering studies for this review

Types of studies An attempt was made to identify all trials which compared synthetic haemodialysis membranes with those made with cellulose or modified cellulose.

Types of participants Any patient maintained on or commencing haemodialysis for ESRD.

Types of intervention Any RCT or quasi-RCT comparing any (or several) synthetic haemodialysis

membranes with any (or several) cellulose or modified cellulose haemodialysis membranes.

Types of outcome measures

1. Symptomatic hypotension or hypotension requiring intervention, headaches, nausea and vomiting, pruritis, anaphylaxis occurring during haemodialysis treatment session (recorded as the number of treatment sessions on which the event occurred).
2. Number of haemodialysis treatments associated with 'any adverse symptoms' if they were not specified with the publication.
3. Number of episodes of significant infection either per patient or per year (diagnosis of and significance of infection as determined by each individual study).
4. Number of hospital admissions and length of stay (as indicator of morbidity and resource use).
5. Adequacy of dialysis measured either by Kt/V or URR.
6. Pre-dialysis β_2 microglobulin concentration.
7. Number of patients with dialysis-associated amyloidosis.
8. Indices of nutritional status: fasting predialysis total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride values, pre-dialysis albumen and PCR.
9. Quality of life.
10. Mortality.

Search strategy for identification of studies

The search strategy used was one developed for the identification of all possible RCTs or quasi-RCTs relating to the management of ESRD, and is described in detail in chapter 2 and appendices 2 and 3.

Methods of the review

All possible RCTs identified on this topic were evaluated using a study evaluation form and those which met the eligibility criteria (included studies) were then considered in detail. Data were extracted using a data abstraction form designed for this review (see appendix 10). Review Manager v. 3.0 was used for the analysis. A full description of the methods used is given in chapter 2.

Description of studies

A total of 21 studies were identified that met the eligibility criteria of being RCTs or quasi-RCTs (*Table 12*). The descriptions of method of allocation published were accepted, and author confirmation was not sought. All studies included have been

published in complete form. Clarification from the authors (Schaefer *et al.*, 1993) of the number of dialysis treatments with each type of membrane was sought and obtained, so that the number of episodes of anaphylaxis per dialysis session could be calculated and entered into Meta-view. A total of 23 trials were excluded because the outcomes were not relevant to this review, and four were excluded because the comparison was not between cellulose and synthetic membranes.

Methodological quality of studies included

Of the 21 studies included (*Table 12*), ten were parallel group randomised trials and 12 were randomised or quasi-randomised crossover studies.

Potential for selection bias at trial entry

The reports of all 21 studies stated that the order of treatment had been randomly allocated. In 16 of these, the method of random allocation used was not described. A secure method of random allocation concealment prior to final trial entry (third party or computer randomisation) was used in three trials (Aakhus *et al.*, 1995; Grooteman *et al.*, 1995; Locatelli *et al.*, 1996); three others (Bergamo Collaboration, 1991; Parker *et al.*, 1996) had potentially insecure methods of random allocation concealment (coin toss with no stated third party involvement and alternation).

Potential for bias in trial analysis

The numbers and reasons for any withdrawals or drop-outs were described in six of the trials (Caramelo *et al.*, 1994; Collins *et al.*, 1993; Hakim *et al.*, 1996; Locatelli *et al.*, 1995; Parker *et al.*, 1996; Schiffel *et al.*, 1995); three (Levin *et al.*, 1993; Skroeder *et al.*, 1994; Ward *et al.*, 1993) mentioned the number of withdrawals and drop-outs but did not give the reasons. The remaining 12 trials did not mention withdrawals or drop-outs.

One trial (Parker *et al.*, 1996) was carried out on an intention-to-treat basis and four (Caramelo *et al.*, 1994; Collins *et al.*, 1993; Hakim *et al.*, 1996; Ward *et al.*, 1993) were not. In the remaining 16 trials, it was not possible to determine whether analysis had been performed on an intention-to-treat basis.

Potential for bias at time of treatment or outcome assessment

In three trials, blinding was mentioned; in one (Aakhus *et al.*, 1995), the membranes were hidden by a covering from the patient and investigator and, in another (Danielson *et al.*, 1986), the patients and healthcare workers were blinded but the method of blinding was not given. There was no blinding in the trial by Gardinali and

TABLE 12 Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes	Notes
Aakhus, et al., 1995	Randomised crossover; randomisation by third party allocation; withdrawals and drop-outs not mentioned; possibly intention-to-treat analysis; blinded effectively for patients and outcomes assessors.	Eight chronic dialysis patients; age range, 24–73 years; M:F 1:1; inclusion and exclusion criteria not stated; co-morbidity: two patients, coronary artery disease; one patient, diabetes; none, ejection fraction < 40%.	One dialysis session – 1 hour haemodialysis, 2 hours ultrafiltration – with each membrane; membranes used: cuprophane (AM-65H-SD; Asahi); Filtral 12 (AN69 HF, Hospal); flux not stated; surface area, not stated; blood flow rate and dialysis flow rate not stated but kept constant; buffer, bicarbonate; EPO, not stated; ACE inhibitor, one patient.	Symptomatic hypotension; URR; echo-cardiographic data.	URR expressed as mean (standard deviation (SD)).
Bergamo Collaboration, 1991	Randomised study with an attempt at concealment (tossing coin); withdrawals and drop-outs not mentioned; patients and healthcare providers well blinded to treatment; no mention of blinding for outcomes assessors; intention-to-treat not clear.	428 patients from six dialysis units who had undergone haemodialysis for ESRD for at least 1 month; mean age, 56.9 years, range 17–79 years (synthetic); 55.9 years, range 19–80 years, cellulose; M:F 93:71, synthetic; M:F, 102:62, cellulose; inclusion criteria – dialysed for at least 1 month; exclusion criteria – acute illness, co-morbidity, diabetes 7 (synthetic); 11 (cellulose).	One dialysis with each membrane, duration as usual for each patient (243 ± 22 minutes, cellulose; 243 ± 19, synthetic); vascular access, not stated; blood flow rate, as usual for patient (mean, 324 ± 33, synthetic; 328 ± 33, cellulose); dialysate flow rate, as usual for patient (mean, 500 ml/min); buffer, acetate or bicarbonate, as usual for patient (bicarbonate – 28 cellulose, 20 synthetic); membrane type – polysulphone (Bellco SPA, Italy), cuprophane (Bellco SPA, Italy), both custom-made with opaque housing, surface area approx. 1 m ² , similar urea and creatinine clearance.	Hypotension requiring treatment; interdialytic headache; interdialytic nausea and vomiting; interdialytic pruritus; interdialytic muscle cramps; β ₂ microglobulin.	Headaches, nausea, vomiting, pruritis recorded as improved, unchanged or worse (post- compared with predialysis). No significant difference between membranes but data not suitable for meta-analysis. β ₂ microglobulin was measured before and after test dialysis; hence, long-term effect could not be judged.
Blankestijn, et al., 1995	Two studies included in paper, but only one relevant; randomised study, states random allocation but no description; withdrawals and drop-outs not mentioned; analysis possibly on intention-to-treat basis but not clear; no mention of blinding of patients, healthcare providers or outcomes assessors.	28 patients stable on haemodialysis, 14 on cuprophane membranes, 14 on synthetic; median age 63 years, range 22–80 years; M:F, 10:18; co-morbidity not stated; inclusion criteria – on chronic haemodialysis for 6 months; exclusion criteria – diabetes or on lipid-lowering drugs.	Duration, 6 weeks with either cuprophane or synthetic membrane; two patients dialysed twice weekly, and 26 patients three times weekly; mean time on dialysis, 11 ± 1.4 hours; blood flow rate and dialysate flow rate not stated – same as usual for each patient; buffer type, bicarbonate; membranes: cuprophane – Asahi AM 140 and 160 Nova, low flux; synthetic – F60S polysulphone high flux (Fresenius); EPO and ACE inhibitor use not mentioned; no reuse.	Predialysis albumin; predialysis triglycerides, cholesterol, lipoprotein A, LDL, HDL.	Main focus was high versus low flux; the second study compared the fall in lipids during dialysis and, as this was not one of our outcome measures, it was not included.

continued

TABLE 12 contd Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes	Notes
Bosch, et al., 1986	Randomised crossover study; randomisation not described; withdrawals and drop-outs not mentioned; possibly intention-to-treat analysis; no mention of blinding for patients, healthcare providers or assessors.	Ten chronic haemodialysis patients; mean age, 54.7 years, range, 38–69 years; M:F, 4:1; co-morbidity, inclusion and exclusion criteria not mentioned.	Three membranes used, each for 2 weeks; duration and frequency of dialysis and vascular access not stated; blood flow, 200 ml/min; dialysate flow, 5000 ml/min; buffer; all acetate; membranes – regenerated cellulose GF120 1.2 m ² (Gambro) hemophan 1.2 m ² (ENKA AG Wupper-tal, FRG) cellulose acetate CDAK 4000, 1.0 m ² (Cordis Dow); EPO and ACE inhibitor use not stated; reuse not stated.	Symptomatic hypotension inter-dialytic – any adverse symptoms; general well-being; adequacy – clearances in ml/minute of urea, creatinine, phosphate but not URR or Kt/V; component of complement, C3a; white blood cells, platelets, elastase α -1 proteinase inhibitor, platelet consumption.	
Caramelo, et al., 1994	Randomised trial; gives random allocation but no description; drop-outs – four from each group, four transplants, four deaths; analysis not intention-to-treat; no mention of blinding of patients, healthcare providers or outcomes assessors.	22 patients with ESRD; none had had transplant; mean age: cellulose, 54 \pm 15 years; synthetic, 46 \pm 16 years; M:F 13:9; exclusions – diabetes, active rapidly-progressing glomerulo nephritis, urine vol < 500 ml/24 hours at start of dialysis, major co-morbid illness (congestive cardiac failure, recent myocardial infarction, chronic obstructive airways disease).	Trial duration, 9 months; duration and frequency of dialysis, vascular access, blood and dialysate flow rate not stated; buffer type: cellulose – nine acetate, four bicarbonate; synthetic – five acetate, four bicarbonate; membranes: cuprophane, PAN, also polysulphone; EPO or ACE inhibitors use not stated; reuse not stated.	Any adverse symptoms, creatinine clearance, urine volumes.	No numerical data suitable for Meta-view.
Collins, et al., 1993	Randomised, crossover study; random allocation not described; number and reasons for drop-outs given – five withdrawals excluded, i.e. not intention-to-treat; no mention of blinding of patients, healthcare providers or outcomes assessors.	35 patients; mean age, cuprophane, 55 years; PAN, 50 years; M:F, 6:14 cuprophane, 7:10 PAN; co-morbidity – nine diabetes, cuprophane: eight diabetes, PAN; inclusion/exclusion criteria not stated.	3 months with each dialysate three times weekly (time not stated); blood flow rate: 300–400 ml/min; dialysate flow rate: 500 ml/min; membranes; cuprophane, surface area 1.6 m ² , UFc 8 ml/mmHg/hour; PAN (AN69), surface area 1.55 m ² , UFc 44 ml/mmHg/hour; EPO and ACE inhibitor use not stated; reuse not stated.	Hypotension, intradialytic headaches, vomiting, pruritus, other symptoms – angina, cramp, broncho-spasm, episodes of infection, hospital admission.	No numerical data given for hospital admissions – states no significant differences were found; episodes of vomiting reported as similar for both membranes using Bonferroni's test, but $p < 0.05$ using t test; this significant on Meta-view, so authors contacted.
Danielson, et al., 1986	Withdrawals and drop-outs not mentioned; randomised, double-blind crossover study; method of allocation not described; patients and staff responsible for dialysis treatment both blinded but methods not stated – possibly intention-to-treat but not clear.	Seven patients, sex not stated, on regular haemodialysis; mean age (SD), 51 (16) years, age range, 30–65 years; co-morbidity not stated; inclusion and exclusion criteria not stated.	Synthetic – polycarbonate (Gambrane); cellulose (Gambro-Lundia), parallel plate; duration of study: polycarbonate, 2 weeks, cuprophane, 4 weeks; duration and frequency of dialysis, 4 hours three times weekly; flux, surface area, dialysate flow rate, blood flow rate, type of buffer, use of ACE inhibitor, and reuse all not stated.	Hypotensive episodes; intradialytic headaches; intradialytic nausea and vomiting; intradialytic pruritus; rise in blood pressure, tachycardia, arrhythmia, chest pain, sweating dyspnoea, muscle cramps, back pain, other pain, anxiety, fever, shivering; anaphylaxis.	* Not clear if patients were asked to report these symptoms or if they were volunteered spontaneously.

continued

TABLE 12 contd Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes	Notes
Gardinali, et al., 1994	Randomised study, states random allocation but no description; withdrawals and drop-outs not stated; possibly carried out on basis of intention-to-treat, but not clear; no blinding of patients, healthcare workers or outcomes assessors.	36 patients (16 cuprophane, 10 PAN, 10 polysulphone); age range, 27–72 years; M:F, 23:13; co-morbidity and inclusion criteria not stated; exclusion criteria, recurrent bacterial infections, diabetes, autoimmune disease and/or myeloma.	Duration of trial, 3 months; duration and frequency, vascular access, blood flow rate and dialysate flow rate not stated; buffer type, bicarbonate; membrane types: cellulose – cuprophane (Nephross Andante 1.0, Organon); polysulphone (BL 627, Bellco, Mirandaola, Italy); polyacrylonitrile (Filtral AN69, Hospal, Meyzieu, France).	β 2 microglobulin levels; components of complement, C3a, C5a; interleukin-1, 2; tumour necrosis factor; s/L-2r; CD3/HLA-DR positive cells + lymphocytes.	Patients on mix of membranes before study began; at start, patients on haemodialysis using cuprophane had higher β 2 microglobulin levels than those using synthetic membranes; at end of study, predialysis levels were 49.7 ± 12.5 (cuprophane), 32.7 ± 9.3 (polysulphone), 35.3 ± 9.4 (PAN), but these not significantly different from those at start of study.
Grooteman, et al., 1995a, b	Randomised crossover trial with good attempt at concealment (computerised); withdrawals and drop-outs not mentioned; possibly intention-to-treat but not clear; no mention of blinding.	31 patients on haemodialysis for at least 6 months; median age, 67 years, range, 27–84 years; M:F, 15:16; co-morbidity – one patient with diabetes; inclusion criteria – on haemodialysis for at least 6 months; exclusion criteria – acute infection, autoimmune disease, malignancy, immunosuppressive drugs, non-steroidal anti-inflammatory drugs.	3 weeks with each membrane; duration of dialysis: 3 or 4 hours, depending on patients' previous prescription; vascular access, not stated; blood flow, 200–250 ml/min; buffer, bicarbonate; membrane types: substituted cellulose-CT 150 G cellulose triacetate (Baxter, Osaka, Japan), flux – UFc, 35, surface area, 1.5 m ² ; synthetic F60 S (Fresenius, Bad Homburg, Germany), flux – UFc, 40, surface area, 1.3 m ² ; EPO and ACE inhibitor use not stated; dialysers not reused.	Kt/V; extraction ratio ($1 - C_{t180}/C_{t0}$) for urea, creatinine, phosphate; β 2 microglobulin predialysis (at end of study); leucocytes, lymphocytes, complement and cytokines.	Significant improvement in Kt/V and extraction ratios for urea, creatinine and phosphate became non-significant when correction made for surface area of membrane.
Hakim, et al., 1996	Multicentre, randomised trial; states random allocation but not described; numbers and reasons for withdrawals and drop-outs given – 37 bioincompatible (BICM) (46%), 56 biocompatible (BCM) (71%); high drop-out rate – 13 (6 BICM:7 BCM) transferred to another centre, 12 (9:3) transplants, 10 (4:6) non-compliant, 29 (4:25) did not achieve Kt/V (includes 16 excluded), 8 (3:5) CAPD, 1 BCM recovered, 16 (4:4) died, 4 (3:1) other reasons; analysis not on intention-to-treat basis; no mention of blinding of patients, healthcare workers or outcomes assessors.	159 patients on chronic haemodialysis; 79 BCM, mean age 51 ± 14 years, 80 BICM, mean age 54 ± 15 years; co-morbidity – no patients excluded on basis of aetiology of renal failure or any other medical condition; inclusion criteria – all patients over 18 years, new to dialysis between 1/3/91 and 31/12/92; exclusion criteria, 16 inadequate Kt/V values in first 2 weeks and data not used.	Duration, 18 months; duration and frequency, vascular access, blood flow rate, dialysate flow rate, and buffer type not stated; membranes: polymethylmethacrylate (PMMA) Toray 32–1.5 H, flux – UFc, 5.0, surface area, 1.7 m ² ; cellulose T175, flux – UFc, 6.0, surface area, 1.5 m ² ; EPO and ACE inhibitor use not stated; re-used, but number of times not specified.	β 2 microglobulin (mg/l) predialysis measured at baseline, and at 3, 6, 7, 12 and 18 months.	High drop-out rate on basis of inadequate Kt/V, particularly in BCM group; very imbalanced.

continued

TABLE 12 contd Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes	Notes
Hosokawa & Yoshida, 1991	Randomised trial, states randomisation but no description; withdrawals and drop-outs not mentioned; analysis possibly on intention-to-treat basis; no mention of blinding of patients, healthcare providers or outcomes assessors.	200 patients on haemodialysis, 100 per membrane; mean age, 52.4 years (PMMA), 53.8 years (cuprophane); M:F, 101:99; co-morbidity and inclusion criteria not stated; exclusion criteria, blood transfusions or vitamin supplements during the study period.	Duration of trial, 1 year; duration and frequency, 5 hours three times per week; membranes: PMMA, cuprophane; EPO, ACE inhibitor use and reuse not stated.	Serum Si, Al, and β_2 microglobulin levels.	It is assumed that 'before' and 'after' treatment refers to the beginning and end of the study period, and not pre- and postdialysis.
Levin, et al., 1993a;b	Randomised crossover trial; random allocation stated but not described; three withdrawals but timing and reasons not given; possibly on intention-to-treat basis but not clear; no mention of blinding of patients, healthcare providers, outcomes assessors.	37 patients at five centres in four countries; mean age 54 years, range 22–78 years; M:F, 23:13; co-morbidity not stated; inclusion criteria, on dialysis for minimum 6 months, stable and compliant, midweek blood urea nitrogen (BUN), 25–32 mmol/l; exclusion criteria, diabetes, no imminent medical problems.	2 weeks with each of seven dialysers; time on dialysis, three times weekly, as follows: Chicago, 3.3 hours, Detroit, 3.1, Osaka, 4.6, Stockholm, 3.9; vascular access, blood flow rate and dialysate flow rate not stated; buffer, acetate; membranes: G10-3N, cuprammonium cellulose, plate 0.8 m ² – cellulose; G120 M cuprammonium cellulose, hollow fibre, 1.2 m ² – cellulose; CD4000 cellulose acetate, hollow fibre, 1.4 m ² – modified cellulose; Duo-flux cellulose acetate, hollow fibre, 1.4 m ² – modified cellulose; T150 PMMA, hollow fibre, 1.4 m ² – synthetic; F60 polysulphone, hollow fibre, 1.25 m ² – synthetic; Filtral copolymer of acrylonitrile and sodium methallyl sulphonate (AN69S), hollow fibre, 1.15 m ² – synthetic; EPO, ACE inhibitor use and reuse not stated.	Symptomatic hypotension, headaches, nausea, vomiting, pruritus, anaphylaxis, chest pain, back pain, dyspnoea, muscle cramps, chills, and fever.	Stated Kt/V measured but results not given; marked variations between centres; used symptoms as reported by staff but not patients.
Locatelli, et al., 1996	RCT; good attempt at concealment, third-party blocked; number and reasons for drop-outs – 164 patients withdrew during 2-year follow-up, 20 died, 22 transplants; two acute clinical reasons, four fistula problems, 29 because of treatment inadequacy, 89 for technical reasons; possible intention-to-treat; no mention of blinding of patients, healthcare providers, outcome assessors.	279 patients; mean age 54.4 (12.8) years, synthetic, 53.16 (12.7) years, cellulose; M:F, 60.5% M, synthetic, 63.6% M, cellulose; co-morbidity, 6.1% with diabetes, synthetic, 4.5% with diabetes, cellulose; inclusion criteria, age range 18–80 years, very stable clinically, RRT \geq 2 months, haemodialysis three times per week, PCR \geq 1.0 g/kg/day; exclusion criteria, malignant disease, no myocardial infarction in last 12 months, no stroke or transient ischaemic event in 6 months, New York Heart Association 3 or 4.	Duration of trial, 24 months; frequency of dialysis, three times weekly; duration, vascular access, blood flow rate, and dialysate flow rate not stated; buffer, bicarbonate; membranes – low flux polysulphone cuprophane; EPO, ACE inhibitor use and reuse not stated.	Symptomatic hypotension, treatment requiring hypotension plus any hypotension all taken together; predialysis albumen; PCR; adequacy (Kt/V); mortality; no hospital admissions and length of stay; predialysis β_2 microglobulin; lipids; transferrin; body weight; skin fold thickness, mid-arm circumference.	Very high drop-out rate, especially for 'technical reasons'; two studies included in this paper; 'hypotension' included those with asymptomatic hypotension.

continued

TABLE 12 contd Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes	Notes
Parker, et al., 1996	Prospective randomised design; randomisation not concealed – alternation; no mention of blinding for patients, healthcare workers or outcomes assessors; withdrawals and drop-outs: BCM, 37/80, BCM, 56/79; reasons for drop-outs: 13 (6 BCM, 7 BCM) transferred to other facilities, 12 (9 BCM, 3 BCM) received transplants, ten (4 BCM, 6 BCM) non-compliant or asked to stop, 29 (4 BCM, 25 BCM) inadequate Kt/V, eight (3 BCM, 5 BCM) changed to peritoneal dialysis, one (BCM) recovered renal function, 16 (8 BCM, 8 BCM) died, four (3 BCM, 1 BCM) dropped out for other reasons.	159 new haemodialysis patients, 80 BCM, 79 BCM; age, 54 ± 15 years (BCM), 51 ± 14 years (BCM); M:F, 50:50; inclusion criteria – over 18 years, new patients; exclusion criteria – none but note many drop-outs; co-morbidity: BCM, 49% with diabetes, 15% with hypertension as aetiology; BCM, 43% with diabetes, 24% with hypertension as aetiology.	Duration of trial, 18 months; duration, frequency, vascular access, blood flow rate, dialysate flow rate and buffer type not stated, left to individual physician; membranes, BCM – PMMA Toray B2-1.5 (Filtrizer Toray Industries), low-level complement activation, low flux; BCM – T175 (Terumo Corporation), high-level complement activation, cellulose; EPO and use of ACE inhibitors not stated; reuse, 10 ± 3.	Pre-dialysis albumin; PCR; Kt/V; mortality; estimated dry weight; pre-albumin; insulin-like growth factor 1.	Drop-out because of inadequate Kt/V in high number on BCM, yet Kt/V was one of the outcomes; overall drop-out rate very high; SDs only given for significantly different albumin values; the value we considered was at 10 months, and at 18 months (end of the study) there was no significant difference.
Quereda, et al., 1988	Randomised crossover study; random allocation stated but no description; withdrawals and drop-outs not mentioned; analysis possibly on intention-to-treat basis; no mention of blinding of patients, healthcare providers or outcomes assessors.	Eight patients; mean age, 58 ± 9 years; M:F, 2:6; co-morbidity – no diabetes or systemic disease; inclusion and exclusion criteria not stated.	Eight phases of 48 sessions each, four sessions of cuprophane and four of PAN; duration and frequency, blood flow rate and dialysate flow rate not stated; buffer – acetate; membranes, cuprophane – hollow fibre, surface area, 0.9 m ² , PAN – flat plate, surface area, 0.7 m ² ; EPO use, ACE inhibitor use and reuse not stated.	Symptomatic hypotension; volume of infused saline.	Symptomatic hypotension may reflect dialysate sodium concentration and temperature rather than membrane type; 'symptomatic hypotension' seemed to be defined as blood pressure < 90 mmHg systolic.
Schaefer, et al., 1993	Randomised crossover study; random allocation stated but no description; withdrawals and drop-outs not mentioned; analysis possibly on intention-to-treat basis; no mention of blinding of patients, healthcare providers or outcomes assessors.	Ten patients on haemodialysis; mean age, 57 years, range, 21–68 years; M:F, 7:3; co-morbidity not stated; inclusion criteria, long-term dialysis patients treated either with cuprophane or polysulphone dialysers; exclusion criteria, patients using ACE inhibitors or with a history of hypersensitivity reactions.	Duration of trial, three dialyses with each dialyser; duration, frequency, vascular access, blood flow rate, dialysate flow rate and buffer type not stated; membranes, cellulose – cuprophane GFE 12 Gambro, 1.3 m ² ; synthetic – AN69 Filtral 12 Hospal, 1.3 m ² , and polysulphone F 60 Fresenius, 1.2 m ² ; membrane fluxes not stated; EPO use not stated; no patients using ACE inhibitors; reuse not stated.	Anaphylaxis; plasma bradykinin.	There was one anaphalactoid reaction in a patient treated with AN69; not possible to add the data as number of dialysis sessions not stated; when authors contacted they stated there were three dialysis treatments with each membrane with sample collection at third treatment.

continued

TABLE 12 contd Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes	Notes
Schiffi, et al., 1995a; b (also in: Mrowka & Schiffi, 1993)	Study B appears to be a randomised trial; claims random allocation but also that 'patients grouped according to their demographic data; definitely not concealed; withdrawals and drop-outs, two transplants and two deaths; possibly on intention-to-treat basis but not clear; no mention of blinding of patients, healthcare providers or outcomes assessors.	24 patients but four drop-outs, two from each group, makes total of 20; age range, 28–69 years (no mean given); co-morbidity and inclusion criteria not stated; exclusion criteria, no infection, autoimmune disease, cancer.	Duration of trial, 72+ months; duration and frequency, 4 hours three times weekly; blood flow rate, dialysis flow rate and buffer not stated; membranes: cellulose – Discap 140, hollow fibre, surface area 1 m ² , low-flux; synthetic – F60 polysulphone, surface area 1.25 m ² , high-flux; EPO use, ACE inhibitor use and reuse not stated.	Predialysis β ₂ microglobulin; carpal tunnel syndrome.	Checking randomisation with authors.
Skroeder, et al., 1993	Randomised crossover study; randomisation method not stated; four withdrawals; not clear if on intention-to-treat basis; no mention of blinding of patients, healthcare providers or outcomes assessors.	20 patients; mean age 59(3) years, range 40–79 years; M:F, 4:1; co-morbidity – no patients had inflammatory, liver or myelo-proliferative disorders; inclusion criteria – stable for at least 3 months on dialysis; exclusion criteria – immuno-suppressed or malignancy, diabetes, acute infection or on anticoagulants.	Three types of membrane used: Cuprophane GF120H (Gambro), surface area, 1.2 m ² ; Hemophan GF120, surface area, 1.2 m ² ; polyamide polyflux, surface area, 1 or 1.6 m ² ; 80–88 dialysis sessions per membrane, 2 or 4 hours equally distributed; blood flow rate, 200–400 ml/min, equally distributed; buffer type, bicarbonate; EPO or ACE inhibitor use not stated; no reuse.	Drop in β ₂ microglobulin concentration per dialysis.	
Skroeder, et al., 1994a; b	Randomised crossover study; randomisation method and withdrawals not stated; possibly on intention-to-treat basis; no mention of blinding of patients, healthcare providers or outcomes assessors.	20 chronic patients on haemodialysis; mean age 61(1) years, range 40–80 years; M:F, 4:1; co-morbidity – immuno-suppression, malignancy, diabetes, anticoagulants, acute infection; inclusion criteria – 3 months stable on dialysis; exclusion criteria – as for co-morbidity.	Three membranes used – cellulose (Cuprophane GM120H, surface area, 1.2 and 2 m ²), Hemophan (GF120, surface area, 1.2–2 m ²), polyamide (Polyflux, surface area, 1 and 0.6 m ²); flux not stated; duration – 77–80 sessions per membrane, 2–4 hours equally distributed; vascular access not mentioned; blood flow rate, 200–400 ml/min equally distributed; dialysate flow rate, 500 ml/min; buffer type, bicarbonate; EPO not used; ACE inhibitor use not stated; no reuse.	Symptomatic hypotension; intradialytic headaches; pruritus; subjective symptoms during dialysis.	Skroeder, et al., 1994b should be excluded because the outcomes are not relevant to this review, although the same patients are studied; Review Manager software is not capable of distinguishing between the two studies.
Vanholder, et al., 1992	Randomised crossover trial; states random allocation, but no description; withdrawals and drop-outs not mentioned; possibly on intention-to-treat basis but not clear; no mention of blinding of patients, healthcare providers or outcomes assessors.	15 new patients on dialysis, seven synthetic, eight cellulose membrane; ages and sex ratio not stated; inclusion criteria – new chronic dialysis patients; exclusion criteria not stated;	Duration of trial, 12 weeks with each dialyser; duration, frequency, vascular access, blood flow rate and dialysate flow rate not stated; buffer type, bicarbonate; membranes: cuprophane either Bravo 501 or Gambro GF20; low flux polysulphone, F-6 Fresenius with minimal complement reactivity; EPO and ACE inhibitor use not stated; no reuse.	No episodes of significant infection; metabolic response to phagocyte stimulus.	

continued

TABLE 12 contd Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes	Notes
Ward, et al., 1993	Randomised crossover study; states random allocation but no description; three drop-outs but no reasons; no mention of blinding of patients, healthcare workers or outcomes assessors.	21 patients at three centres; mean ages, 62 ± 12 years (centre 1), 53 ± 6 years (centre 2), 37 ± 8 years (centre 3); overall M:F, 62:38; co-morbidity not stated; inclusion criteria – stable on three times weekly dialysis, β_2 microglobulin > 35 mg/l; exclusion criteria – evidence of infection, haematocrit level $< 18\%$.	Duration, 2 weeks (6 treatments) with each dialyser; duration and frequency, three times weekly but time variable; vascular access not stated; blood flow rate, 200 ml/min (centre 3 kept it at this level for first hour only); dialysate flow rate, 500 ml/min; buffer type, 18 bicarbonate, three acetate; membranes: cuprophane – D2 Fresenius, surface area, 1.1 m^2 , six patients; GF180M Gambro, surface area, 1.6 m^2 , six patients; GFS120 Gambro, surface area, 1.1 m^2 , one patient; L10-5N Gambro, surface area, 1.1 m^2 , seven patients; L10-6N Gambro, surface area, 1.6 m^2 , one patient; modified cellulose – Haemophan HP Nikkiso, surface area, 1.2 m^2 , 21 patients; synthetic – AN69 (Filtral 12) Hospal, surface area, 1.15 m^2 , 21 patients; EVAL (KF 101N) Kuraray, surface area, 1.3 m^2 , 21 patients; EPO and ACE inhibitor use not stated; reuse, 6 times.	Intradialytic pruritus (sessions of no dialysis not stated, so data not in Meta-view); three patients on EVAL membrane; URR.	β_2 microglobulin clearance measured and was similar in high-flux modified cellulose and synthetic but both were greater than cuprophane; study authors suggest this may reflect flux rather than synthetic nature of membrane.

colleagues (1994). In the remaining 18 trials, no mention was made of blinding.

Our quality assessment tool assumes that the avoidance of bias is best achieved by an RCT with:

- secure concealment of allocation before formal trial entry
- adequate blinding of patients, outcomes assessors and healthcare providers
- description of reasons and numbers of withdrawals and drop-outs
- analysis on an intention-to-treat basis.

None of the trials fulfilled all of these criteria.

Other characteristics of included studies

All the studies were published in English; 15 were published between 1993 and 1996, three in 1991 and 1992, and three in the late 1980s. The majority of trials were thus relatively recent and, for the most part, described membranes in current use.

Ten studies commented on the co-morbid illnesses present in the dialysis patients and eight excluded patients on the basis of co-morbidity, although the nature of the excluding conditions varied from study to study.

In some studies, it was not possible to derive data for the outcome measure in question, either because outcomes were not given in numerical form at all or because they were not given in sufficient detail (e.g. means given without standard deviations or standard errors). When this occurred it is described in the Results (below).

Results

For the purpose of this review, when cellulose membranes were compared with synthetic membranes, the cellulose membranes were regarded as the controls. Similarly, when modified cellulose membranes were compared with synthetic, the

TABLE 13B Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Number of haemodialysis treatments associated with symptomatic or treatment-requiring hypotension					
Cellulose membrane					
Aakhus, 1995	1/8	1/8		0.3	1.00 (0.06, 17.62)
Bergamo, 1991	39/214	32/214		8.6	1.27 (0.76, 2.11)
Collins, 1993	187/1260	180/1260		45.2	1.05 (0.84, 1.30)
Danielson, 1986	1/12	1/6		0.2	0.45 (0.02, 9.33)
Levin, 1993	75/645	42/422		14.4	1.19 (0.80, 1.76)
Querada, 1988	71/192	82/192		13.3	0.79 (0.52, 1.18)
Skroeder, 1994	3/77	5/80		1.1	0.62 (0.15, 2.55)
Subtotal (95% CI)	377/2411	343/2179		83.1	1.03 (0.88, 1.21)
Chi-square 3.60 (df = 6) Z = 0.38					
Modified cellulose membrane					
Levin, 1993	75/645	54/428		15.7	0.91 (0.63, 1.33)
Skroeder, 1994	3/77	6/77		1.2	0.49 (0.13, 1.89)
Subtotal (95% CI)	78/722	60/505		16.9	0.87 (0.61, 1.25)
Chi-square 0.74 (df = 1) Z = 0.75					
Total (95% CI)	455/3133	403/2684		100.0	1.00 (0.86, 1.16)
Chi-square 5.03 (df = 8) Z = 0.04					
Number of haemodialysis treatments associated with headaches					
Cellulose membrane					
Collins, 1993	24/1260	30/1260		11.9	0.80 (0.46, 1.37)
Danielson, 1986	0/6	3/12		0.5	0.18 (0.01, 2.35)
Levin, 1993	152/645	96/422		41.1	1.05 (0.78, 1.40)
Skroeder, 1994	5/77	12/80		3.4	0.42 (0.15, 1.14)
Subtotal (95% CI)	181/1988	141/1774		57.0	0.92 (0.72, 1.18)
Chi-square 4.96 (df = 3) Z = 0.66					
Modified cellulose membrane					
Levin, 1993	152/645	88/428		40.3	1.19 (0.89, 1.59)
Skroeder, 1994	5/77	8/77		2.7	0.61 (0.20, 1.88)
Subtotal (95% CI)	157/722	96/505		43.0	1.14 (0.86, 1.51)
Chi-square 1.27 (df = 1) Z = 0.90					
Total (95% CI)	328/3133	237/2684		100.0	1.01 (0.84, 1.22)
Chi-square 7.48 (df = 5) Z = 0.09					
<i>continued</i>					

TABLE 13B contd Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Number of haemodialysis treatments associated with nausea/vomiting					
Cellulose membrane					
Collins, 1993	68/1260	108/1260		40.6	0.61 (0.45, 0.83)
Danielson, 1986	0/6	0/12		0.0	Not estimable
Levin, 1993	81/645	78/422		32.1	0.63 (0.44, 0.88)
Subtotal (95% CI)	149/1911	186/1694		72.7	0.62 (0.49, 0.78)
Chi-square 0.01 (df = 1) Z = 4.10					
Modified cellulose membrane					
Levin, 1993	81/645	50/428		27.3	1.09 (0.75, 1.58)
Subtotal (95% CI)	81/645	50/428		27.3	1.09 (0.75, 1.58)
Chi-square 0.00 (df = 0) Z = 0.43					
Total (95% CI)	230/2556	236/2122		100.0	0.72 (0.59, 0.88)
Chi-square 6.31 (df = 2) Z = 3.27					
0.1 0.2 1 5 10 Favours treatment Favours control					
Number of haemodialysis treatments associated with pruritis					
Cellulose membrane					
Collins, 1993	14/1260	10/1260		4.6	1.40 (0.63, 3.13)
Danielson, 1986	0/6	0/12		0.0	Not estimable
Levin, 1993	205/645	154/422		44.2	0.81 (0.62, 1.05)
Skroeder, 1994	9/77	6/80		2.6	1.62 (0.56, 4.68)
Subtotal (95% CI)	228/1988	170/1774		51.4	0.88 (0.69, 1.12)
Chi-square 2.94 (df = 2) Z = 1.03					
Modified cellulose membrane					
Levin, 1993	205/645	174/428		45.6	0.68 (0.53, 0.88)
Skroeder, 1994	8/77	9/77		3.0	0.88 (0.32, 2.39)
Subtotal (95% CI)	213/722	183/505		48.6	0.69 (0.54, 0.88)
Chi-square 0.24 (df = 1) Z = 2.95					
Total (95% CI)	441/2710	353/2279		100.0	0.78 (0.66, 0.93)
Chi-square 5.13 (df = 4) Z = 2.79					
0.1 0.2 1 5 10 Favours treatment Favours control					

continued

TABLE 13B contd Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Number of haemodialysis treatments associated with anaphylaxis					
Cellulose membrane					
Danielson, 1986	0/12	1/12		52.9	0.14 (0.00, 6.82)
Schaefer, 1993	1/60	0/30		47.1	4.48 (0.07, 286.51)
Subtotal (95% CI)	1/72	1/42		100.0	0.70 (0.04, 12.17)
Chi-square 1.44 (df = 1) Z = 0.24					
Modified cellulose membrane					
Subtotal (95% CI)	0/0	0/0		0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00					
Number of haemodialysis treatments associated with adverse symptoms					
Cellulose membrane					
Danielson, 1986	3/6	1/12		4.8	9.75 (0.99, 96.31)
Skroeder, 1994	18/77	22/80		49.0	0.81 (0.39, 1.65)
Subtotal (95% CI)	21/83	23/92		53.8	1.01 (0.51, 1.99)
Chi-square 4.14 (df = 1) Z = 0.02					
Modified cellulose membrane					
Skroeder, 1994	18/77	19/77		46.2	0.93 (0.45, 1.95)
Subtotal (95% CI)	18/77	19/77		46.2	0.93 (0.45, 1.95)
Chi-square 0.00 (df = 0) Z = 0.19					
Total (95% CI)	39/160	42/169		100.0	0.97 (0.59, 1.60)
Chi-square 4.17 (df = 2) Z = 0.12					
Number of patients who had an episode of significant infection					
Cellulose membrane					
Vanholder, 1992	0/7	3/8		100.0	0.11 (0.01, 1.30)
Subtotal (95% CI)	0/7	3/8		100.0	0.11 (0.01, 1.30)
Chi-square 0.00 (df = 0) Z = 1.75					
Modified cellulose membrane					
Subtotal (95% CI)	0/0	0/0		0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00					
Total (95% CI)	0/7	3/8		100.0	0.11 (0.01, 1.30)
Chi-square 0.00 (df = 2) Z = 1.75					

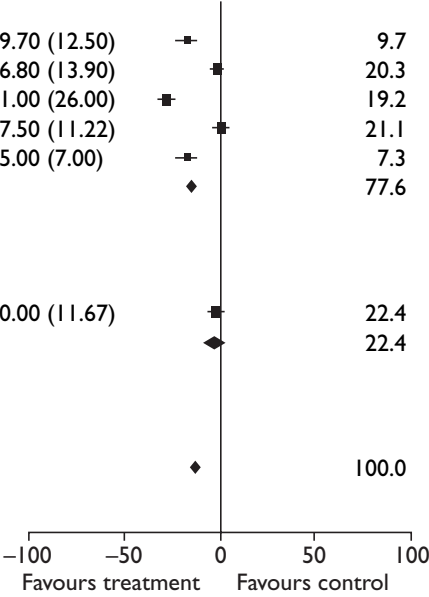
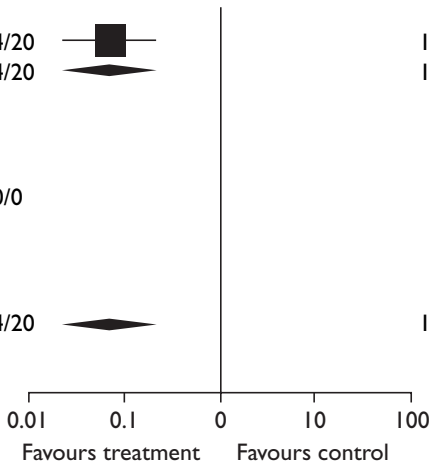
continued

TABLE 13B contd Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Number of hospital admissions per year							
Cellulose membrane							
Locatelli, 1996	147	0.50 (1.20)	132	0.40 (0.80)		100.0	0.100 (-0.137, 0.337)
Subtotal (95% CI)	147		132			100.0	0.100 (-0.137, 0.337)
Chi-square 0.00 (df = 0) Z = 0.83							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							
Total (95% CI)	147		132			100.0	0.100 (-0.137, 0.337)
Chi-square 0.00 (df = 0) Z = 0.83							
Number of days in hospital							
Cellulose membrane							
Locatelli, 1996	147	4.70 (11.50)	132	4.00 (10.00)		100.0	0.700 (-1.823, 3.223)
Subtotal (95% CI)	147		132			100.0	0.700 (-1.823, 3.223)
Chi-square 0.00 (df = 0) Z = 0.54							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							
Total (95% CI)	147		132			100.0	0.700 (-1.823, 3.223)
Chi-square 0.00 (df = 0) Z = 0.54							
Kt/V							
Cellulose membrane							
Locatelli, 1996	59	-1.35 (0.25)	56	-1.32 (0.20)		40.5	-0.030 (-0.113, 0.053)
Parker, 1996	79	-1.24 (0.27)	80	-1.37 (0.29)		36.4	0.130 (0.043, 0.217)
Subtotal (95% CI)	138		136			77.0	0.046 (-0.014, 0.106)
Chi-square 6.83 (df = 1) Z = 1.50							
Modified cellulose membrane							
Grooteman, 1995a	31	-0.97 (0.22)	31	-1.08 (0.22)		23.0	0.110 (0.000, 0.220)
Subtotal (95% CI)	31		31			23.0	0.110 (0.000, 0.220)
Chi-square 0.00 (df = 0) Z = 1.97							
Total (95% CI)	169		167			100.0	0.061 (0.008, 0.113)
Chi-square 7.85 (df = 2) Z = 2.26							

continued

TABLE 13B contd Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Predialysis β2 microglobulin serum concentration (mg/l)							
Cellulose membrane							
Gardinali, 1994	10	32.70 (9.30)	16	49.70 (12.50)	-	9.7	-17.000 (-25.411, -8.589)
Hakim, 1996	23	34.00 (10.00)	43	36.80 (13.90)	■	20.3	-2.800 (-8.628, 3.028)
Hosokawa, 1991	100	42.00 (16.00)	100	81.00 (26.00)	■	19.2	-39.000 (-44.984, -33.016)
Locatelli, 1996	59	37.50 (19.20)	56	37.50 (11.22)	■	21.1	0.000 (-5.713, 5.713)
Schiffi, 1995	10	37.00 (14.00)	10	55.00 (7.00)	-	7.3	-18.000 (-27.702, -8.298)
Subtotal (95% CI)	202		225		◆	77.6	-14.217 (-17.195, -11.239)
Chi-square 105.89 (df = 5) Z = 9.90							
Modified cellulose membrane							
Grooteman, 1995a	31	27.00 (10.56)	31	30.00 (11.67)	■	22.4	-3.000 (-8.540, 2.540)
Subtotal (95% CI)	31		31		◆	22.4	-3.000 (-8.540, 2.540)
Chi-square 0.00 (df = 0) Z = 1.06							
Total (95% CI)	233		256		◆	100.0	-11.703 (-14.326, -9.080)
Chi-square 117.66 (df = 5) Z = 8.74							
							
Number of patients with dialysis-associated amyloidosis							
Cellulose membrane							
Schiffi, 1995	0/20		14/20		■	100.0	0.05 (0.01, 0.18)
Subtotal (95% CI)	0/20		14/20		◆	100.0	0.05 (0.01, 0.18)
Chi-square 0.00 (df = 0) Z = 4.58							
Modified cellulose membrane							
Subtotal (95% CI)	0/0		0/0			0/0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							
Total (95% CI)	0/20		14/20		◆	100.0	0.05 (0.01, 0.18)
Chi-square 0.00 (df = 0) Z = 4.58							
							

continued

TABLE 13B contd Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Total cholesterol concentration							
Cellulose membrane							
Blankestijn, 1995	14	4.71 (0.95)	14	5.20 (0.57)		100.0	-0.490 (-1.070, 0.090)
Subtotal (95% CI)	14		14			100.0	-0.490 (-1.070, 0.090)
Chi-square 0.00 (df = 0) Z = 1.65							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							
HDL cholesterol concentration							
Cellulose membrane							
Blankestijn, 1995	14	-0.81 (0.16)	14	-0.88 (0.19)		100.0	0.070 (-0.060, 0.200)
Subtotal (95% CI)	14		14			100.0	0.070 (-0.060, 0.200)
Chi-square 0.00 (df = 0) Z = 1.05							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							
LDL cholesterol concentration							
Cellulose membrane							
Blankestijn, 1995	14	2.87 (0.73)	14	2.99 (0.59)		100.0	-0.120 (-0.612, 0.372)
Subtotal (95% CI)	14		14			100.0	-0.120 (-0.612, 0.372)
Chi-square 0.00 (df = 0) Z = 0.48							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							

TABLE 13B contd Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Triglyceride concentration							
Cellulose membrane							
Blankestijn, 1995	14	1.82 (0.59)	14	2.48 (0.80)		100.0	-0.660 (-1.181, -0.139)
Subtotal (95% CI)	14		14			100.0	-0.660 (-1.181, -0.139)
Chi-square 0.00 (df = 0) Z = 2.48							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							
Serum albumin concentration (g/dl)							
Cellulose membrane							
Blankestijn, 1995	14	-3.30 (0.33)	14	-3.50 (0.44)		11.7	0.200 (-0.088, 0.488)
Locatelli, 1996	59	-4.00 (1.54)	56	-4.00 (1.12)		4.0	0.000 (-0.490, 0.490)
Parker, 1996	79	-3.89 (0.34)	80	-3.73 (0.35)		84.3	-0.160 (-0.267, -0.053)
Subtotal (95% CI)	152		150			100.0	-0.111 (-0.210, -0.013)
Chi-square 5.47 (df = 2) Z = 2.22							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							
PCR							
Cellulose membrane							
Locatelli, 1996	59	-1.22 (0.24)	56	-1.24 (0.24)		100.0	0.020 (-0.068, 0.108)
Subtotal (95% CI)	59		56			100.0	0.020 (-0.068, 0.108)
Chi-square 0.00 (df = 0) Z = 0.45							
Modified cellulose membrane							
Subtotal (95% CI)	0		0			0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00							

continued

TABLE 13B contd Synthetic vs. cellulose/modified cellulose haemodialysis membranes: detailed meta-analysis

Study	Patient n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Mortality					
Cellulose membrane					
Locatelli, 1996	12/147	8/132		56.2	1.37 (0.55, 3.40)
Parker, 1996	8/79	8/80		43.8	1.01 (0.36, 2.84)
Subtotal (95% CI)	20/226	16/212		100.0	1.20 (0.61, 2.37)
Chi-square 0.18 (df = 1) Z = 0.53					
Modified cellulose membrane					
Subtotal (95% CI)	0/0	0/0		0.0	Not estimable
Chi-square 0.00 (df = 0) Z = 0.00					
Total (95% CI)	20/226	16/212		100.0	1.20 (0.61, 2.37)
Chi-square 0.18 (df = 1) Z = 0.53					

0.1 0.2 1 5 10
Favours treatment Favours control

(1996) excluded patients with recent evidence of cardiovascular and cerebrovascular disease and malignant disease.

Levin and colleagues (1993) reported hypotension as noted by the staff and as 'problems with blood pressure' reported by patients; for this study, data from staff reporting were entered into Meta-view in line with two other trials that used this outcome measure and which mentioned the method of reporting. The patients reported blood pressure problems very much more frequently (143/645 sessions on synthetic membranes and 137/422 sessions on cellulose membranes; there was no mention of blinding of patients or staff) and if these data had been used, the results of the study by Levin and colleagues would have achieved statistical significance in favour of synthetic membranes, although the overall results would just have failed to reach significance. Patients also reported symptoms more frequently when treated with modified cellulose membranes (118/428). Had these results been entered, significantly fewer episodes of symptomatic hypotension would have been reported with synthetic membranes for this study and for the overall meta-analysis.

Number of haemodialysis treatments associated with headache

Four trial reports include headache as an outcome measure. There was no evidence of significant heterogeneity between these trials and, overall, there was no statistically significant difference be-

tween cellulose and synthetic membranes. For this outcome, the patient-reported data from the study by Levin and colleagues (1993) were entered; had the number of headaches reported by the staff been used (25/645 synthetic and 7/422 cellulose), there would have been no change in the overall result. Two papers compared modified cellulose membranes with synthetic membranes; there was no evidence of significant heterogeneity between the trials and no difference in the incidence of headaches.

Number of haemodialysis treatments associated with nausea/vomiting

Three trials compared nausea and vomiting between cellulose and synthetic membranes. One very small trial (Danielson *et al.*, 1996) showed no episodes of nausea or vomiting with either treatment, and two other trials (Collins *et al.*, 1993; Levin *et al.*, 1993), using patient-reported data, showed significantly less nausea and vomiting with synthetic membranes. There was no evidence of heterogeneity between the trials and reflecting this, the overall effect confirmed significantly less nausea and vomiting when a synthetic membrane was used (OR, 0.62; 95% CI, 0.49, 0.78). 'Numbers-needed-to-treat' (NNT) analysis indicated that in 31 (95% CI, 20, 78) dialysis sessions there would be one fewer episode of nausea or vomiting using a synthetic membrane.

Only one trial compared modified cellulose with synthetic membranes (Levin *et al.*, 1993) and no

significant difference was found for this outcome. This trial included patients with diabetes, although no other description of co-morbidity was given.

Meta-analysis of the studies showed a significantly lower incidence of nausea and vomiting with synthetic membranes compared with cellulose and modified cellulose membranes.

Number of haemodialysis treatments associated with pruritus

Four papers considered pruritus as an outcome measure. There was no evidence of heterogeneity and no overall significant differences between cellulose and synthetic membranes. Levin and colleagues study (1993), using patient-reported data, just failed to reach statistical significance in favour of synthetic membranes. Two trials compared this outcome between modified cellulose and synthetic membranes. There was no evidence of significant heterogeneity and there was a significant difference in favour of synthetic membranes in the trial by Levin and colleagues and when the results of the two studies were combined (NNT, 15; 95% CI, 8, 71). Although in the trial by Levin and colleagues, staff reported fewer cases of pruritus overall (22/645 synthetic, 19/422 modified cellulose), the estimate of risk reduction (OR, 0.75) is similar to that derived from patient-reported symptoms. The overall estimate for all trials, for both cellulose and modified cellulose, should be interpreted with caution because it is largely dependent on a single trial (Levin *et al.*, 1993) and the data from the group treated with synthetic membranes in this trial were counted twice because it was a three group comparison.

Number of haemodialysis treatments associated with anaphylaxis

Anaphylaxis was mentioned in the reports of only two trials; a single case was reported among those managed with a synthetic membrane, and a single case after use of a synthetic membrane. Patients on angiotensin converting enzyme (ACE) inhibitors were excluded from the trial by Schaefer and colleagues (1993), and were not mentioned in the earlier trial, carried out at a time when such drugs were not readily available.

Number of haemodialysis treatments associated with any adverse symptoms

Two papers commented on 'unspecified adverse symptoms' in numerical form. One trial was very small and, overall, there was no evidence of any difference. Another paper (Caramelo *et al.*, 1994) commented that there were no adverse symptoms in patients being treated with either membrane but did not give any numerical data.

Number of patients who had an episode of significant infection

Relevant data on infection were available for only 15 patients (van Holder *et al.*, 1992), of whom three were reported to have had significant infections.

Number of hospital admissions per year and number of days of hospital admission per year

The large trial by Locatelli and colleagues (1996) was the only one to report hospital admissions; no difference between cellulose and synthetic membranes was found. The methodology of this trial was well described but excluded many patients with co-morbid illness, particularly cardiovascular disease. The number of hospital admission days per year was also similar between the two groups.

Kt/V

Two trials showed values for Kt/V in patients treated with cellulose or synthetic membranes; Parker and colleagues (1996) showed a difference between the membranes that favoured the cellulose membrane, Locatelli and colleagues (1996) did not but excluded two patients with a Kt/V value of < 0.95 (lower than required for inclusion in the study). Both studies used low-flux membranes. Meta-analysis of these studies failed to show a significant benefit for either of these membranes for this outcome measure. The trials did, however, display heterogeneity, perhaps because of their exclusion criteria, different policies for reuse, and duration of dialysis session (not reported).

One trial compared Kt/V for synthetic and modified cellulose membranes (Grooteman *et al.*, 1995). The lower value for the synthetic group is of borderline statistical significance; the flux, as measured by the ultrafiltration coefficient (UFc), of the two membranes was again reported by the authors to be similar (UFc = 35, modified cellulose; UFc = 40, synthetic).

Meta-analysis of all three studies just reached statistical significance in favour of cellulose and modified cellulose membranes.

Urea reduction ratio

One trial (Ward *et al.*, 1993), which compared cellulose, modified cellulose and synthetic membranes, measured URR. However, standard deviations were not given and the WMD could not be calculated. When cellulose membranes were compared with two synthetic membranes, the URR was slightly higher for those dialysing with cellulose membranes (mean URR cellulose membrane,

60%; mean URRs synthetic, 55%, 54%). When a modified cellulose membrane was compared with synthetic membranes, the mean URR values were 52%, 55% and 54%, respectively. The authors concluded that the cellulose membrane had a greater clearance than the others ($p = 0.013$).

Predialysis β 2 microglobulin serum concentration and amyloid disease development

Five groups measured predialysis β 2 microglobulin serum concentrations at the beginning and end of their trials when comparing cellulose with synthetic membranes; there was evidence of significant heterogeneity between studies, probably due to differences in flux. Overall, there was a significant decrease in β 2 microglobulin values when synthetic membranes were used. However, two studies (Hakim *et al.*, 1996; Locatelli *et al.*, 1996) showed no significant improvement with synthetic membranes and they are characterised by the use of cellulose and synthetic membranes with a similar low flux. The trials, which showed a significantly lower concentration of β 2 microglobulin with the synthetic membrane at the end of the study period, all compared high-flux synthetic membranes with low-flux cellulose membranes. The trials varied in length from 3 months (Gardinali *et al.*, 1994) to 72 months (Schiffli *et al.*, 1995).

In one trial (Grooteman *et al.*, 1995), modified cellulose membranes were compared with synthetic membranes. There was no significant difference in predialysis β 2 microglobulin serum concentration between these membranes, both of which had similar high-flux characteristics.

In a further trial, Schiffli and colleagues (1993) compared the development of amyloid disease over a 6-year period and found significantly less amyloid disease occurring with the synthetic membranes (the sample size was, however, small); no cases of amyloid disease were seen using the synthetic membrane. The authors point out again that the synthetic membrane had a high UFc whereas that for the cellulose membrane was low.

Predialysis lipids

In one trial, Blankestijn and colleagues (1995) measured predialysis plasma total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides over a 6-week period. Of these, only the serum triglyceride concentration in the group assigned a synthetic membrane was significantly lower. The synthetic membrane had high-flux characteristics and the cellulose membrane low-flux characteristics. In another study, Locatelli and colleagues (1996)

commented that there was no statistically significant difference in plasma cholesterol or triglycerides in patients dialysed with cellulose or synthetic membranes in the 24-month follow-up period of their trial. Both these membranes were low flux.

Serum albumin concentration

Three trials reported serum albumin concentrations. In the largest, Parker and colleagues (1996) showed a significantly higher mean level in the group using synthetic membranes and the overall estimate reflects this one trial. The trial by Blankestijn and colleagues (1995) excluded patients with diabetes and that of Locatelli and colleagues (1996) patients who had had a recent myocardial infarct or who had a history of stroke or transient ischaemic attack. Parker and colleagues included patients with diabetes in their trial. Meta-analysis of the three studies showed a significant difference in serum albumin concentration in favour of synthetic membranes.

Protein catabolic rate

PCR was only reported in one trial and there was no significant difference between the membranes used.

Mortality

The trials by Parker and colleagues (1996) and Locatelli and colleagues (1996) both had mortality as an outcome measure. The trial by Parker and colleagues lasted 18 months and there were eight deaths in each group. Locatelli and colleagues quote deaths at their 24-month follow-up as 12/147 (18%) in patients dialysed with low-flux synthetic membranes and 8/132 (12%) in those dialysed with cellulose membranes. In neither trial nor in the overall meta-analysis was there a significant difference between cellulose and synthetic membranes.

Discussion

Overall, this systematic review indicates that the incidence of nausea and vomiting was less with synthetic than with cellulose membranes, and that the incidence of pruritis was less with synthetic membranes than with modified cellulose membranes. Predialysis β 2 microglobulin concentrations were significantly lower at the end of the studies in patients treated with synthetic membranes also, although all studies which showed this effect used high-flux synthetic membranes. Similarly, one study showed the incidence of amyloid disease to be less in patients who were dialysed for 6 years with high-flux synthetic membranes. In the one study in which triglyceride values were measured,

there was a significant effect in favour of the synthetic high-flux membrane. Serum albumin concentrations were higher in patients treated with synthetic membranes (of both high and low flux). There was no significant difference between these membranes for any other outcomes measures.

Many types of membranes are now manufactured; 128 'commonly used dialysers' are currently listed in the *Handbook of Dialysis* (2nd edition; Daugirdas & Ing, 1994). They vary in surface area, clearance of various molecules, UFc, and geometry (hollow fibre or parallel plate) as well as in the material from which they are manufactured. Biocompatibility is generally believed to be a property of the material of the membrane and the higher the biocompatibility, the fewer the blood-membrane interactions releasing complement and activating leucocytes. Whether such reactions lead to clinical sequelae such as malnutrition and infection is not clear (Bauremeister *et al.*, 1989). Synthetic membranes are more biocompatible and have, therefore, been made with a larger surface area. They are also generally more porous and, hence, suitable for more rapid removal of water and molecules larger than urea and creatinine, particularly β_2 microglobulin, persistently high concentrations of which are believed to result in the development of amyloid over a period of years in dialysis patients. This correlation, however, is still in some doubt (Cheung, 1990). Synthetic membranes with high-flux characteristics and also, possibly, with an ability to absorb substances such as β_2 microglobulin on their surfaces are used to shorten dialysis time; this is popular both with patients and with busy dialysis units, although rapid fluid removal may result in hypotension. However, this was not shown in this review. The beneficial effect of synthetic membranes on serum albumin levels, however, occurred in trials using both high- and low-flux membranes.

It is somewhat disappointing, therefore, given the plethora of membranes and the claims made for them, that more large well-planned RCTs which take into account the material of the membrane and its flux have not been undertaken. In particular, relatively few trials have been performed which used the outcome measures of symptoms felt by patients.

A total of 22 RCTs were identified (*Table 12*) which had clinical outcome measures as their end-points, and some data from most of them have contributed to this review. Levin and colleagues' detailed trial (1993) shows that a given symptom is recorded more frequently when patients rather than staff are asked to undertake recording. We

had to choose which results to display, although both were calculated for the four outcome measures. For hypotension, data from staff were shown; patient data favoured the synthetic membrane in this study and the aggregated result almost achieved statistical significance. For the other outcomes (headache, nausea and vomiting, pruritis) patient-recorded data were displayed, although the relative risk reductions (ORs) were generally similar whichever type of data were used. Most trials did not mention the method of symptom recording. Recording of symptoms is subjective and in future trials should be explicit and predominantly patient-based, with blinding of the patients and the staff to the treatment where possible.

Significant heterogeneity between trials was noted for three outcome measures, most notably β_2 microglobulin concentrations. This may have been because both low- and high-flux membranes were used and significant improvement was only seen with synthetic membranes when high-flux membranes were used. β_2 microglobulin was used as a surrogate for amyloidosis, which takes many years to develop, and in the one 6-year study found, the incidence of amyloidosis was less with a high-flux synthetic membrane.

The co-morbid illnesses of patients taking part in the trials were mentioned in some but not all studies. It is possible to argue that biocompatible membranes may be more suitable for patients with complex illnesses but also that the low-flux, long dialysis carried out with cellulose membranes may also be beneficial for some patients, particularly those with cardiovascular instability. It would be useful, given the increasing co-morbidity of dialysis patients, to be able to address these issues in secondary stratified analysis but data to allow this are not currently available. It would be particularly useful to study modified cellulose membranes which can be made with a higher flux than standard cellulose membranes (UFc, approximately 15) and synthetic membranes with a similar flux.

Trials in which cellulose was compared with synthetic membranes and for which Kt/V was reported as an outcome measure were significantly heterogeneous. When cellulose and modified cellulose membranes together were compared with synthetic membranes, Kt/V was just significantly lower in the latter. Duration of dialysis session, however, was not given in all studies and this, together with the heterogeneity, makes it difficult to draw any conclusions. In one study, Hakim and colleagues (1996) used inadequate Kt/V in the first 2 weeks of the trial as an exclusion criterion,

although not as an outcome measure. Locatelli and colleagues (1996) excluded two patients because the Kt/V value was < 0.95 . Furthermore, in studies in which the methodology was described in some detail (Hakim *et al.*, 1996; Locatelli *et al.*, 1996) there was a large drop-out rate because of transfer of patients to another modality of dialysis, transplantation, transfer to another centre, non-compliance and, in one study, not achieving an adequate Kt/V. Variation within the studies is, therefore, a major limitation of this review.

The management of end-stage renal failure is a high technology speciality for relatively few patients at great cost. Therefore, trials tend to be on small groups of patients whose numbers are further reduced by the drop-out rates as detailed above. Because of the high cost of dialysis, RCTs are a valuable means of decision-making in this area. They require, however, large numbers of patients with prolonged follow-up, so that the longer-term implications which are important to patients can be adequately measured.

Surrogate outcome measures such as complement levels are more likely than primary outcome measures to change significantly over the course of a short study, are easier to measure and, hence, are more frequently undertaken. There is a real need, as others in the field have already suggested (Bauremeister *et al.*, 1989; Daugirdas, 1994; Churchill, 1995; Locatelli *et al.*, 1996), for further large multicentre studies. Such trials should state the patients' co-morbid illnesses and, perhaps, stratify them before trial entry such that the most effective membranes for all types of patient can be determined. The trials should be designed to evaluate the role of flux, as well as the material from which the membrane is made, and should have sufficient follow-up for clinical outcomes to be measured. In this manner, it could be determined whether the new membranes which are being rapidly developed have improved the effectiveness over previously available membranes for patients or sub-groups of patients on haemodialysis.

Economic evaluation

Introduction

The principles of economic evaluation are described in detail in chapter 3 (page 9) including, in an economic framework, the manner in which costs and outcome are related (see, in particular, *Table 2* and *Figure 3*).

Aims

It is possible that synthetic membranes offer additional benefits over cellulose or modified cellulose membranes for the dialysis of patients with ESRD. The relative efficiency of these alternatives will be investigated using the framework of economic evaluation outlined. More specifically, the aims of this economic evaluation are:

- (i) to investigate the relative resources used and the costs of synthetic, cellulose or modified cellulose membranes using data extracted from the identified RCTs and non-randomised studies in which the three type of membranes are compared
- (ii) to combine data on cost differences with data on differential effectiveness from the systematic review of effectiveness described above in order to assess the relative efficiency of dialysing patients with synthetic, cellulose, or modified cellulose membranes.

Methods

Data collection

The methods used are described in detail in chapter 2 of the main report.

Benefits to patients

The systematic review of RCTs or quasi-RCTs synthesised data on the effectiveness of various membranes. The outcome measures were as follows.

1. Symptomatic hypotension or hypotension requiring intervention, headaches, nausea and vomiting, pruritis, anaphylaxis occurring during haemodialysis treatment session (recorded as the number of treatment sessions on which the event occurred).
2. Number of haemodialysis treatments associated with 'any adverse symptoms' if they were not specified with the publication.
3. Number of episodes of significant infection either per patient or per year (diagnosis of and significance of infection as determined by each individual study).
4. Number of hospital admissions and length of stay (as indicator of morbidity and resource use).
5. Adequacy of dialysis measured either by Kt/V or URR.
6. Pre-dialysis β_2 microglobulin concentration.
7. Number of patients with dialysis-associated amyloidosis.
8. Indices of nutritional status: fasting predialysis total cholesterol, HDL cholesterol, LDL

cholesterol and triglyceride values, predialysis albumen and PCR.

9. Quality of life.
10. Mortality.

Identification of resource use and costs

The overall cost of haemodialysis using the various membranes was not given in any of the available information. Differences in resource use (and thus cost) between delivery of haemodialysis under different policies for use of membranes was therefore assessed in four stages.

1. The definition of the process of care, so that all relevant items of resource use could be identified.
2. For each part of the process of care (e.g. the dialysis session, the treatment of complications) in which resource use was believed to be different, data on resource use were abstracted from the publications of trials in the effectiveness review.
3. Similar data were abstracted from non-randomised studies obtained from the economic search.
4. The information on resource use (obtained from stages 2 and 3) was then combined with information on the unit cost of the resources to determine the cost differential between the various membranes using methodology described below. This differential could then be compared with the difference in effectiveness.

Model of costs

Dialysis session The information from the 22 RCTs included in the effectiveness review showed that the same equipment and dialysate could be used for both types of membranes and the sessions, where stated, were similar in duration (see following references in the list of studies included (page 71): Aakhus *et al.*, 1995; Bergamo Collaboration, 1991; Danielson *et al.*, 1986; Grooteman *et al.*, 1995; Hosokawa & Yoshida, 1991; Mrowka & Schiffli, 1993; Skroeder *et al.*, 1993; 1994). Therefore any difference in the cost of the dialysis is due solely to the different cost of the membrane used.

Treatment of complications The relative cost of treating complications with the different membranes was also estimated using decision analysis (*Figure 9*) (Lapin, 1991). It is assumed in this analysis that when a particular complication occurs treatment is always provided. Data on the proportion of patients that had a specific complication such as pruritus or amyloidosis were abstracted from the identified RCTs, which provided the most robust estimates available. These were used to estimate the probability that a patient would receive

treatment for a complication in a set period (either per session, per week or per month). The RCTs and the non-randomised studies were used to identify more precisely the resources used in treatment of a specific complication. The treatments were then costed according to the staff, consumables, overheads and capital that the treatment consumed. The estimates of staff time were taken from a study conducted in the USA (Jones, 1992) in which a panel of clinicians and nurses were sampled and asked for estimates of staff time for selected clinical vignettes of complications of haemodialysis (which included some of the complications in which we are interested). This paper provided upper and lower estimates of staff time and so allowed upper and lower estimates to be calculated for the costs of complications. No such data were available from a UK source. The prices of any pharmaceuticals consumed were taken from the BNF (1996), and the cost of staff time was estimated by combining information on time with that from the relevant UK NHS salary scales (NHS, 1996a; b). An important assumption of this type of model is that the probability of having a complication (and therefore, receiving treatment) is independent of the probability of having any other type of complication.

Results

Benefits to patients

The systematic review of effectiveness compared:

- (i) synthetic membranes as the experimental treatment and cellulose membranes as the control
- (ii) synthetic membranes as the experimental treatment and modified cellulose membranes as the control.

For these two comparisons no significant differences were found for dialysis treatments associated with hypotension or with headache, anaphylaxis, any adverse symptoms, hospital admissions, significant infection, mortality, PCR or Kt/V. There were also no significant differences in fasting pre-dialysis serum total cholesterol concentration, LDL cholesterol concentration or HDL cholesterol concentration (see general references to this appendix).

Fasting pre-dialysis serum triglyceride concentration was significantly lower in patients dialysed with synthetic membranes compared with cellulose membranes, and nausea and vomiting were also less. The results of the one available trial showed no significant differences between the incidence of nausea and vomiting in patients treated with synthetic and modified cellulose membranes. A significant difference was reported favouring

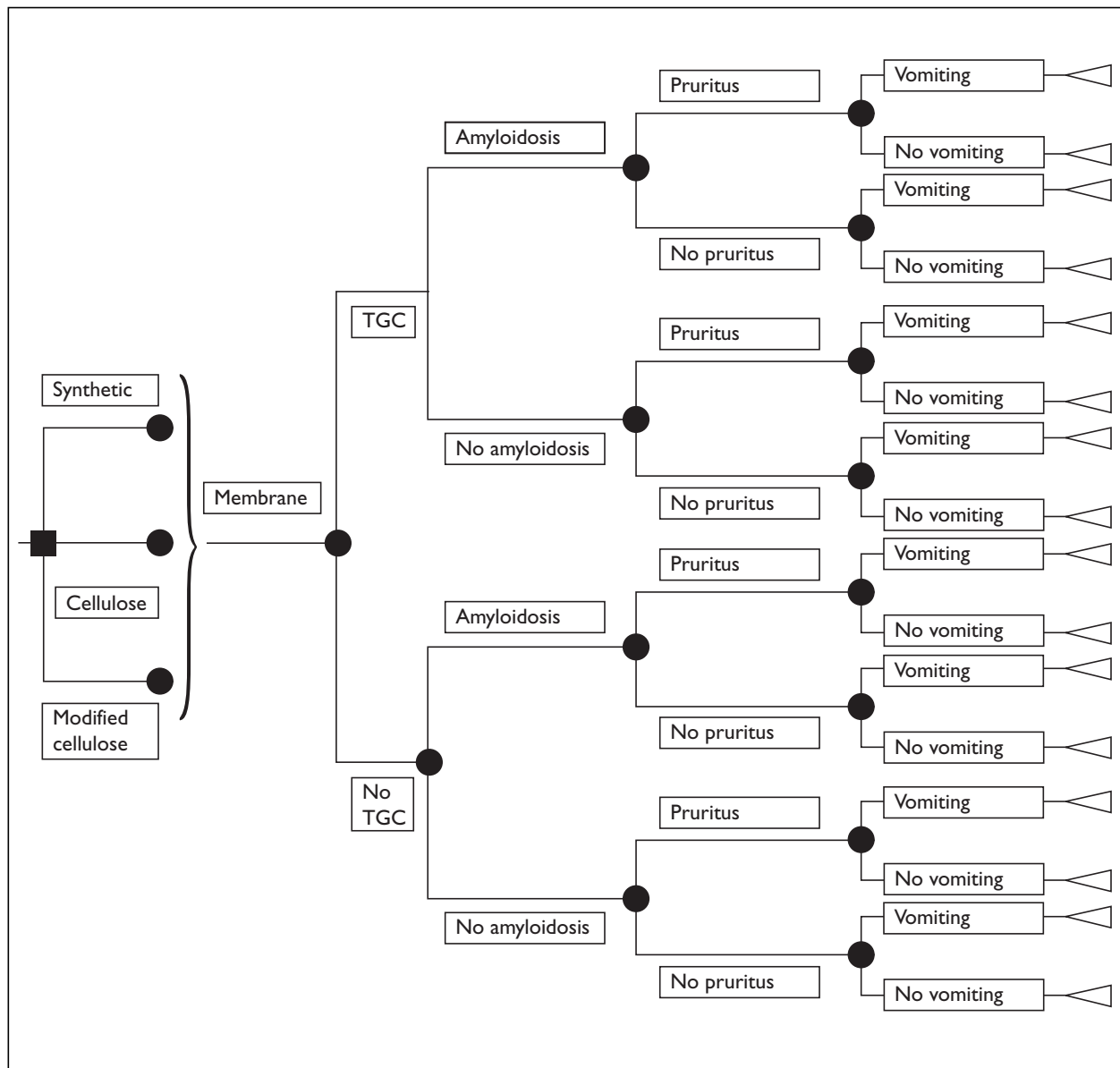


FIGURE 9 Decision model to compare the alternative forms of haemodialysis (■, decision node; ●, chance node; ◁, terminal node; TGC = triglyceride concentration)

synthetic over modified cellulose membranes in respect of patients' assessments of the number of treatments associated with pruritus. No such difference was found when episodes of pruritus were reported by staff who would initiate treatment.

There was a significant reduction in pre-dialysis β_2 microglobulin serum concentration when synthetic membranes were used compared with cellulose membranes. The trials that showed a significant difference between synthetic and cellulose membranes were comparing high-flux synthetic membranes with low-flux cellulose membranes. In the two papers reporting no significant difference, both used membranes of similar low flux. For the comparison of synthetic with modified cellulose membranes, no significant difference was reported.

The development of amyloidosis was significantly less common in those managed with synthetic membranes compared with those managed with cellulose membranes.

Resource use and costs

Estimates of the costs of membranes were obtained from the manufacturers (primarily from Gambro Ltd) and from information obtained from Aberdeen Royal Hospitals NHS Trust. A range of costs (low, medium and high) is shown in *Table 14* with upper estimates based upon companies' price lists and lower costs based upon estimates of the prices paid by hospital providers.

Cost estimates for complications were obtained by combining the staff time estimates with the

TABLE 14 The cost of haemodialysis membranes

Cost	Type of membrane		
	Synthetic (£ per membrane)	Modified cellulose (£ per membrane)	Cellulose (£ per membrane)
Low	10	7.5	7.5
Medium	20		
High	29	12	10.5

relevant pay scales and the cost of any consumables (Table 15). The cost of treating pruritus has not been calculated as there was no significant difference in the recording of pruritus per dialysis session by healthcare providers, although patients assessed that there were more episodes with cellulose than synthetic membranes. It has been assumed that treatment would only be provided if the healthcare provider knew of the problem. Amyloidosis is a long-term condition that may require surgical interventions (possibly many years later) to relieve some of its symptoms. The cost of such interventions and the time delay before they occurred were not determined as no data were identified on which to base estimates. Information would be required on the form of intervention, the time delay before the intervention is given and the proportion of patients that would require treatment. Also required would be data on the outcome of any intervention.

The probabilities for the occurrence of complications described in the systematic review of effectiveness are shown in Table 16. The higher the probability, the greater the chance of that complication occurring. There was insufficient evidence of any differences in the rate of complications when synthetic membranes were compared with modified cellulose membranes.

Using the data contained in Tables 15 and 16 the cost of complications can be calculated using the

TABLE 15 Staff costs of complications per session

Complication	Staff time (hours)		Consumable cost (£)	Cost per session (£)	
	Low	High		Low	High
Vomiting	0.25	0.75	0.50	3.47	8.86

TABLE 16 The probabilities of complications occurring when there was a significant difference in outcome between synthetic and cellulose membranes (per treatment)

Condition	Cellulose	Synthetic
Amyloidosis	0.7	0
Nausea and vomiting	0.075	0.047

framework shown in Figure 9. This information can then be combined with that on the cost of membranes (see Table 14). The results of this are shown in Table 17 for cellulose compared with synthetic membranes. When modified cellulose and synthetic membranes were compared, no differences were found between complications that would require treatment. The only cost differences remaining are those between the costs of the membranes themselves.

TABLE 17 The cost per dialysis session of cellulose membranes compared to synthetic membranes

	Type of membrane				
	Cellulose (£ per dialysis session)		Synthetic (£ per dialysis session)		
	Low cost	Price list	Low cost	Medium cost	Price list
Cost of membrane	7.5	10.5	10	20	29
Cost of complications	0.55	0.55	0.34	0.34	0.34
Total cost	8.05	11.05	10.34	20.34	29.34

Combining costs and benefits

The combination of the information on the relative effectiveness and cost of haemodialysis using synthetic versus modified cellulose or cellulose membranes can provide information on the relative efficiency of the two alternatives. Overall, there is greater cost and insufficient evidence of effectiveness (area C4 on matrix in Figure 3), and thus there is insufficient evidence to recommend managing patients with haemodialysis using synthetic membranes in preference to cellulose or substituted cellulose membranes. Such information that is available tends to suggest that haemodialysis using synthetic membranes provides more benefits to patients than haemodialysis using modified cellulose or cellulose membranes. If this is assumed to be the case, it would be achieved at greater cost

(area C1 on matrix, *Figure 3*) and a judgement would be required as to whether the synthetic membranes are worth the extra cost.

Additional information can be obtained from the data by using incremental analysis, to identify the extra resources required to achieve one additional unit of a beneficial effect. An estimate of the extra cost required to prevent an extra case of nausea and vomiting can be calculated to be between £90 and £680 avoided. These figures do not account for other benefits beyond the prevention of nausea and vomiting shown for synthetic membranes. Using the data in *Table 14* and assuming three dialysis sessions per week it can be calculated that the total additional annual cost per patient of using synthetic membranes lies between £390 [$(£10 - £7.50) \times 3 \times 52$] and £3354 [$(£29 - £7.50) \times 3 \times 52$] (with the higher value based upon manufacturers' price lists for synthetic membranes). These calculations exclude the costs of complications.

For the comparison of synthetic membranes with modified cellulose membranes only one outcome was significantly different – the reduction of patient-reported episodes of pruritus. Using incremental analysis it is possible to estimate that it would cost between £37.5 and £255 per case of pruritus averted when synthetic are used in preference to modified cellulose membranes.

Discussion

The limitations of the evidence on effectiveness discussed in the preceding section must be borne in mind when interpreting this review. We have chosen to concentrate on differences that have reached statistical significance and it should be remembered that lack of statistical significance does not necessarily equate with no difference. Certainly, most confidence intervals for the estimated effects do not rule out clinically important differences.

The data used to estimate the relative efficiency of the alternative membranes also have to be treated with some caution. Costs are derived from estimates of resource use which are taken from different studies and which may not be generalisable to others. A further issue is that for this review not all potential complications were included in the calculation of costs. The cost of treating amyloidosis remains uncertain and further work is required to identify whether synthetic membranes offer some protection against the development of this condition compared with cellulose and modified cellulose membranes. If such differences do exist

then the costs and benefits of such treatment need evaluation.

There is insufficient data available on effectiveness for a judgement to be made on the relative efficiency of the different membranes. If such data that we have are accepted then the implication would be that synthetic membranes are both more effective for certain outcomes and more costly than either cellulose or modified cellulose membranes. A judgement would be required as to whether the additional benefits are worth the additional costs, since the additional resources can only be obtained by reducing potentially beneficial services elsewhere.

One problem when making this judgement is that it is not possible to amalgamate the many measures of effectiveness into a single unitary value. Therefore, ratios of incremental cost to incremental effectiveness fail to formally take into account the many different aspects of benefits that are provided.

Conclusions

The conclusions are drawn from both the systematic review of effectiveness and the economic evaluation.

Implications for clinical practice

1. End-of-study β_2 microglobulin values and the development of amyloid disease were less in patients treated with synthetic membranes compared with cellulose membranes. Plasma triglyceride values were also lower with synthetic membranes in the single study that measured this outcome. These outcomes may have reflected the high flux of the membrane. Nausea and vomiting were less with synthetic membranes (both low and high flux) and serum albumin concentrations were higher. Pruritus was recorded less frequently with synthetic than with modified cellulose membranes.
2. We are hesitant to recommend the universal use of synthetic membranes for haemodialysis in patients with ESRD on the basis of the above results because of the small numbers of trials, particularly for modified cellulose membranes (many with low patient numbers); the heterogeneity of many of the trials compared; the variations in membrane flux, and the differences in exclusion criteria, particularly relating to co-morbidity. In this review we found insufficient information to perform a satisfactory economic evaluation. Such evidence as there is favours synthetic membranes but the extra

benefit would currently be at considerable cost, particularly if high-flux membranes were to be used.

Implications for research

Further pragmatic RCTs are required to compare the different dialysis membranes available. They are required:

- (i) to take into account other properties, including flux, as well as the material from which the membrane is manufactured, and to test modified cellulose membranes as well as standard ones
- (ii) to record the minimum of data, concentrating on primary outcomes of major importance to patients and on patient preference
- (iii) to explicitly record whether symptoms of patient- or staff-reported, while recognising that, in general, patient reporting will be more appropriate for evaluating effectiveness but staff reporting may be necessary for calculating the cost of treating complications
- (iv) to be multicentre (and possibly multi-national) in order to have sufficient patients for the trial to be completed despite considerable numbers of withdrawals and drop-outs
- (v) to have sufficiently long follow-up for conclusions to be drawn on important clinical outcome measures; they should continue to follow patients who withdraw because they receive a transplant
- (vi) to include older patients and those with co-morbid illnesses and to take these into account when assessing outcomes (possibly by stratification at trial entry)
- (vii) to have performed, in parallel, an economic evaluation of the different policies being compared in the trial.

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Schiffel H, Kuchle C, Held E, 1995b. Beta-2-microglobulin removal by different hemodialysis membranes. *Contrib Nephrol*;112:156–63.

Skroeder NR, Jacobson SH, Holmquist B, Kjellstrand P, Kjellstrand CM, 1993. Beta 2-microglobulin generation and removal in long slow and short fast hemodialysis. *Am J Kidney Dis*;21:519–26.

Skroeder NR, Jacobson SH, Lins LE, Kjellstrand CM, 1994a. Acute symptoms during and between hemodialysis: the relative role of speed, duration, and biocompatibility of dialysis. *Artif Organs*;18:880–7.

Skroeder NR, Kjellstrand P, Holmquist B, Kjellstrand CM, Jacobson SH, 1994b. Individual differences in biocompatibility responses to hemodialysis. *Int J Artif Organs*;17:521–30.

Vanholder R, van Landschoot N, Waterloos MA, Delanghe J, van Maele G, Ringoir S, 1992. Phagocyte metabolic activity during hemodialysis with different dialyzers not affecting the number of circulating phagocytes. *Int J Artif Organs*;15:89–92.

Ward RA, Schaefer RM, Falkenhagen D, Joshua MS, Heidland A, Klinkmann H, *et al.*, 1993. Biocompatibility of a new high-permeability modified cellulose membrane for haemodialysis. *Nephrol Dial Transplant*;8:47–53.

Studies excluded from the review (with reason for exclusion)

Azikawa T, Kitaoka T, Koshikawa S, Watanabe T, Imamura K, Tsurumi T, *et al.*, 1986. Development of a regenerated cellulose non-complement activating membrane for hemodialysis. *Trans Am Soc Artif Intern Organs*;32:76–80.

(Described cellulose versus modified cellulose with no synthetic membranes studies.)

Churchill DN, Taylor DW, Tomlinson CW, Beecroft ML, Gorman J, Stanton E, *et al.*, 1993. Effect of a high-flux hemodialyses on cardiac structure and function among patients with end-stage renal failure [published erratum appears in *Nephron* 1994;66:469]. *Nephron*;65:573–7.
(Only compared similar membranes differing in permeability.)

Combe C, Pourteim M, de Precigout V, Baquay A, Morel D, Portaux L, *et al.*, 1994. Granulocyte activation and adhesion molecules during hemodialysis with cuprophane and a high-flux biocompatible membrane. *Am J Kidney Dis*;24:437–42.

(Outcomes not relevant to this review.)

de Broe ME, van Waelegheem JP, Heyrman R, de Backer W, 1986. Biocompatibility of a polycarbonate membrane. A preliminary report. *Blood Purif*;4:168–71.

(Outcomes not relevant to this review.)

de Broe ME, de Backer WA, Verpooten GA, Vermeire PA, van Waelegheem JP, Herman AG, 1983.

(Outcomes not relevant to this review.)

Himmelfarb J, Ault KA, Holbrook D, Leeber DA, Hakim RM, 1993. Intradialytic granulocyte reactive oxygen species production: a prospective, crossover trial. *J Am Soc Nephrol*;4:178–86.

(Outcomes not relevant to this review – studied granulocyte reactive oxygen species production and response to stimuli.)

Ivanovich P, Hammerschmidt DE, Quintanilla A, Kishimoto T, Tanaka H, Levin N, *et al.*, 1993. Behaviour of platelets and beta-thromboglobulin. *Nephrol Dial Transplant*;8 suppl 2:15–19.

(Outcomes not relevant to this review.)

Kishimoto T, Tanaka H, Maekawa M, Ivanovich P, Levin N, Bergstrom J, *et al.*, 1993. Dialysis-induced hypoxaemia. *Nephrol Dial Transplant*;8 suppl 2:25–9.

(Outcomes not relevant to this review – looked at pH, PO₂, PCO₂.)

Kramer BK, Pickert A, Hohmann C, Liebich HM, Muller GA, Hablitzel M, *et al.*, 1992. In vivo clearance and elimination of nine marker substances during hemofiltration with different membranes. *Int J Artif Organs*;15:408–12.

(Outcomes not relevant to this review – studied β₂ microglobulin but only looked at the fall in levels across dialysis.)

Moll S, de Moerloose P, Reber G, Schifferli J, Leski M, 1990. Comparison of two hemodialysis membranes, polyacrylonitrile and cellulose acetate, on complement and coagulation systems. *Int J Artif Organs*;13:273–9.

(Outcomes not relevant to this review.)

Navarro J, Serrano C, Donna E, Perez GO, 1992. Disordered breathing patterns during bicarbonate hemodialysis in COPD. Effect of cuprophane versus polysulfone membranes. *ASAIO J*;38:811–14.

(Outcomes not relevant to this review – studied pulmonary function.)

Opatrny K Jr, Sulkova S, Lopot F, Vit L, Valek A, Opatrny K, 1993. Clinical study of high-flux cuprammonium rayon hemodialysis membranes. *Artif Organs*;17:971–6.

(Only different fluxes compared.)

Sanaka T, Higuchi C, Shinobe T, Nishimura H, Omata M, Nihei E, *et al.*, 1995. Lipid peroxidation as an indicator of biocompatibility in haemodialysis. *Nephrol Dial Transplant*;10:34–8.

(Outcomes not relevant to this review.)

Schaefer RM, Kulzer P, Gilge U, Schaefer L, Heidland A, 1994. Clinical evaluation of the new, steam-sterilized polysulfone high-flux dialyzer. *Clin Nephrol*;42 suppl 1:S21–5.

(Comparison of three synthetic membranes only.)

Schmitt GW, Moake JL, Rudy CK, Vicks SL, Hamburger RJ, 1987. Alterations in hemostatic parameters during hemodialysis with dialyzers of different membrane composition and flow. *Am J Med*;83:411–18.

(Outcomes not relevant to this review – studied platelet loss and activation, Factor VIII-related von Willebrand factor and 6-keto-prostaglandin.)

Skroeder NR, Kjellstrand P, Holmquist B, Kjellstrand CM, Jacobson SH, 1995. On complement net generation in fast hemodialysis: are high blood flow rates bioincompatible? *Am J Kidney Dis*;25:896–903.

(Outcomes not relevant to this review.)

Strasser T, Schiffel H, 1991. Generation of leukotriene B₄ by hemodialyzer membranes: a novel index of biocompatibility. *Klin Wochenschr*;69:808–12.

(No clinical end-points and none relevant to this review – studied leukotriene B₄.)

Stuard S, Carreno M-P, Poignet J-L, Albertazzi A, Haeffner-Cavaillon N, 1995. A major role for CD62P/CD15s interaction in leukocyte margination during hemodialysis. *Kidney Int*;48:93–102.

(Outcomes not relevant to this review – studied adhesion molecule expression, leucocyte counts, platelet activation.)

Thylen P, Lundahl J, Fernvik E, Hed J, Svenson SB, Jacobson SH, 1992. Mobilization of an intracellular glycoprotein (Mac-1) on monocytes and granulocytes during hemodialysis. *Am J Nephrol*;12:393–400.

(Outcomes not relevant to this review.)

Tridon A, Deteix P, Coves G, Cluzel P, Marques Vendier A, Wauquier JP, *et al.*, 1987. [Evaluation of the biocompatibility of a new cellulose membrane by studying the complement system and histamine liberation] (in French). *Nephrologie*;8:217–21.

(Outcomes not relevant to this review.)

Vanholder R, Ringoir S, Dhont A, Hakim R, 1991. Phagocytosis in uremic and hemodialysis patients: a prospective and cross-sectional study. *Kidney Int*;39:320–7.

(Outcomes not relevant to this review – studied phagocytosis; did not mention clinical episodes of septicaemia but were the same as in Vanholder *et al.*, 1992.)

Verbeelen D, Jochmans K, Herman AG, van der Niepen P, Sennsael J, de Waele M, 1991. Evaluation of platelets and haemostasis during haemodialysis with six different membranes. *Nephron*;59:567–72.

(Outcomes not relevant to this review – studied platelet count, plasma fibrinopeptide A, β thromboglobulin, von Willebrand factor antigen and 6-keto-prostaglandin F_{1 α} .)

Wehle B, Bergstrom J, Kishimoto T, Lantz B, Levin N, Klinkmann H, 1993. Beta 2-microglobulin and granulocyte elastase. *Nephrol Dial Transplant*;8 suppl 2:20–4.

(Considered β 2 microglobulin but only after six dialyses with the membrane; studied the difference between pre- and postdialysis β 2 microglobulin.)

General (including economics) references

Baris E, McGregor M, 1993. The reuse of hemodialyzers: an assessment of safety and potential savings [published erratum appears in *Can Med Assoc J* 1993;148:1278]. *Can Med Assoc J*;148:175–83.

Bauermeister U, Vienken J, Ansorge W, Luttrell A, 1989. Cellulosic versus synthetic membranes: a reasonable comparison? *Artif Organs*;13:52–7.

British Medical Association and The Pharmaceutical Press, 1996. British National Formulary (September 1996). Bath: Bath Press.

Cheung AK, 1990. Biocompatibility of haemodialysis membranes. *J Am Soc Nephrol*;1:150–61.

Churchill DN, 1995. Clinical impact of biocompatible dialysis membranes on patient morbidity and mortality: an appraisal of the evidence. *Nephrol Dial Transplant*;10 suppl 10:52–6.

Daugirdas JT, 1994. The possible effects of dialyzer membrane on morbidity and mortality [review]. *Nephrol Dial Transplant*;9 suppl 2:145–9.

Daugirdas JT, Ing TS, 1994. Handbook of dialysis. 2nd edition. Boston: Little, Brown; chap 3.

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Hakim R, 1993. Clinical implications of hemodialysis membrane biocompatibility. *Kidney Int*;44:484–94.

Jones K, 1992. Variations in the haemodialysis treatment process. *Clin Nurs Res*;1:50–66.

Lapin L, 1991. Quantitative methods for business decisions: with cases. 5th edition. Orlando: Harcourt Brace Javanovich College Publishers.

NHS, 1996a. Pay and conditions of service: remuneration of hospital, medical and dental staff and doctors in public health medicine and the community health service. Edinburgh: Scottish Office: National Health Service in Scotland, NHS circular PCS (DD)1996/4.

NHS, 1996b. Nurses and midwives pay for 1996/97. Special duty payments, leads and other allowances. Edinburgh: The Scottish Office: National Health Service in Scotland, NHS circular PCS (NM)1996/3.

Ward RA, Buscaroli A, Schmidt B, Stefoni S, Gurland HJ, Klinkman H, 1997. A comparison of dialyzers with low-flux membranes: significant differences in spite of many similarities. *Nephrol Dial Transplant*;12:965–72.

Appendix 5

Systematic review 2: Comparison of bicarbonate-buffered with acetate-buffered dialysate in haemodialysis as treatment for patients with ESRD

Background

Patients with end-stage renal failure require either dialysis (haemodialysis or peritoneal dialysis) or a renal transplant to maintain life. Haemodialysis achieves its purpose of replacing renal function by passing the patient's blood through a dialyser containing a semi-permeable membrane. Dialysate is passed through the dialyser on the opposite side of the membrane. This membrane allows certain substances to pass through it by the process of diffusion. Substances normally excreted by the kidney, such as urea and potassium, which are in relatively high concentrations in the blood, will diffuse into the dialysate and be removed from the body.

One of the critical functions of dialysis is the correction of the metabolic acidosis caused by the diseased kidney's failure to excrete non-volatile acids and to regenerate bicarbonate. A buffer is therefore added to the dialysate to correct the metabolic acidosis. This buffer passes across the semi-permeable membrane from the dialysate into the blood. Bicarbonate is the natural buffer normally regenerated by the kidneys and was the initial choice as dialysate buffer in the 1940s and 1950s. However, if sodium bicarbonate is added to a calcium- or magnesium-containing dialysate, their respective carbonate salts will precipitate unless the dialysate is maintained at a low pH level. Dialysate concentrate containing calcium or magnesium was therefore stored separately from bicarbonate-containing dialysate concentrate. When both were mixed with water to produce the final dialysate, carbon dioxide was bubbled through the dialysate to lower its pH level and thus avoid precipitation of the salts. These procedures demanded extra storage, equipment and labour.

In 1964, Mion used acetate as an alternative buffer (Mion, *et al.*, 1964). Acetate is rapidly converted to bicarbonate in the liver through the action of the enzyme acetyl CoA synthetase. From a practical

point of view, acetate offered the major advantage of not precipitating calcium or magnesium in the dialysate; it quickly replaced bicarbonate as the standard dialysate buffer and remained so for the next 20 years.

In the late 1970s and early 1980s, a number of studies suggested that some of the morbidity associated with haemodialysis could be attributed to the acetate component of the dialysate (Novello, 1976; Aizawa, 1977). This morbidity particularly referred to intra- and post-haemodialysis symptoms such as nausea, vomiting, muscle cramps, headaches, symptomatic hypotension, poor appetite and cardiovascular instability. Patients on haemodialysis have a markedly increased prevalence of atherosclerotic vascular disease and it was suggested that acetate may contribute to this by its adverse effect on lipid metabolism (Tolchin, 1979). Renal bone disease may be a source of significant morbidity for dialysis patients and, by its poorer correction of metabolic acidosis, acetate dialysate may contribute to its progression.

The dialysis-associated symptoms which had been attributed to 'acetate intolerance' appear to have been unmasked by the introduction of high-efficiency and short-duration dialysis using membranes with large surface areas. This movement towards high-efficiency dialysis was particularly marked in the USA.

Acetate intolerance led to the reappraisal of bicarbonate as a dialysis buffer in the early 1980s and, following the solving of technical difficulties, to its reintroduction. Initially it was reintroduced specifically for patients thought to be more prone to the adverse effects of acetate, such as those who had previously demonstrated acetate intolerance, those with acute renal failure and those with known cardiovascular instability. It was also used for patients with possibly impaired acetate metabolism, such as those with reduced muscle mass, diabetes mellitus and liver disease. In addition,

bicarbonate dialysate was used for those undergoing high-efficiency dialysis in which large surface area membranes may allow a greater mass transfer of acetate than the liver is readily able to metabolise.

From these early specific indications, bicarbonate dialysate rapidly became generally used for all haemodialysis patients in many countries.

The use of bicarbonate dialysis in preference to acetate dialysis initially had significant cost implications. However, today, because nearly all haemodialysis machines can use either acetate or bicarbonate dialysate with no modification, and because of the increased use of bicarbonate, the cost differential between acetate and bicarbonate dialysis may no longer apply.

The purpose of this review was to identify whether bicarbonate dialysis is to be preferred to acetate dialysis for the haemodialysis of patients with ESRD.

Objectives

The objectives of this review were to compare bicarbonate dialysis with acetate dialysis for the haemodialysis of patients with ESRD by testing the following hypotheses:

- (i) that bicarbonate haemodialysis reduces the frequency of adverse symptoms during dialysis compared with acetate dialysis
- (ii) that bicarbonate haemodialysis improves cardiovascular stability during dialysis compared with acetate haemodialysis
- (iii) that bicarbonate haemodialysis improves lipid profile compared with acetate haemodialysis
- (iv) that bicarbonate haemodialysis slows the progression of renal bone disease compared with acetate haemodialysis.

The cost implications of using bicarbonate haemodialysis instead of acetate haemodialysis were also examined.

Materials and methods

Criteria for considering studies for this review

Types of studies An attempt was made to identify all trials in which bicarbonate (experimental group) was compared with acetate (control group) in the haemodialysis of patients with ESRD and in which patients were prospectively randomly

(e.g. sealed envelopes with third party involvement) or quasi-randomly (alternate patients or alternate treatments) allocated to either treatment. Cross-over trials in which treatments alternated to at least the degree A–B–A–B were also included, even if the allocation to first treatment was neither random nor quasi-random.

Types of participants Patients with ESRD who were maintained on haemodialysis were eligible, irrespective of age, sex, race, primary renal disease or co-morbidity. Trials which exclusively comprised patients with acute renal failure were excluded. Each individual study's definition of ESRD or maintenance haemodialysis was accepted.

Types of intervention In the experimental group haemodialysis was against a predominantly bicarbonate-buffered dialysate, while in the control group it was against a predominantly acetate-buffered dialysate. Only haemodialysis was considered and any form of haemofiltration was excluded.

Types of outcome measures

1. Intra- and postdialytic symptoms: frequency of nausea, vomiting, headaches, muscle cramps, symptomatic or treatment-requiring hypotension; any assessment of patient acceptability, well-being or quality of life.
2. Intradialytic cardiovascular stability: changes in blood pressure, cardiac output and peripheral vascular resistance.
3. Correction of metabolic acidosis: pre-, intra- and postdialysis pH level, P_{CO_2} and bicarbonate concentrations.
4. Indicators of renal bone disease: serum calcium, phosphate and parathyroid hormone concentrations.
5. Lipid profile: fasting cholesterol and triglycerides.

Search strategy for identification of studies

The search strategy used was one developed for the identification of all possible RCTs or quasi-RCTs relating to the management of ESRD, and is described in detail in chapter 2 and appendices 2 and 3.

Methods of the review

Identified studies were evaluated using a study evaluation form and those which met the eligibility criteria (included references) were then considered in detail. Data were extracted using a data abstraction form designed for this review (see appendix 10). Review Manager v. 3.0 was used

for the analysis. A full description of the methods used is given in chapter 2.

Description of studies

A total of 18 studies were identified which met the eligibility criteria of being RCTs or quasi-RCTs. The Antwerp trial in 1983 was subsequently considered as two separate trials (de Backer, *et al.*, 1983); in addition to being randomised to bicarbonate or acetate dialysis, patients had also been randomised to dialysis with a polyacrylonitril or a cuprophane membrane. Similarly, the Hamilton trial in 1983 was subsequently considered to be two separate studies (Shimizu, *et al.*, 1983) as patients had also been randomised to high sodium or low sodium dialysate. The descriptions of method of allocation published were accepted and no confirmation was sought from the authors. In cases where the same study had been published more than once, only the most recent data were used. If more than one relevant study was published in the same paper, each study was listed and analysed separately. All the studies included were published in full except for the Philadelphia study in 1985 (Brezin, *et al.*, 1985), which was only available as an abstract. Only published data from the studies were used. Seven of the studies could not be included in the quantitative analyses because the recorded measures outcome differed from those specified. This indicates the wide variation in recorded measures of outcome for essentially similar outcomes demonstrated across the studies. The studies are summarised in *Table 18*.

A total of 30 crossover studies which were not randomised or quasi-randomised or did not demonstrate alternation at least to the degree A–B–A–B are listed as excluded studies. No further analyses of these studies were made.

Methodological quality of included studies

All 18 included studies were of crossover design, although in the 1983 Paris study (Lefebvre, *et al.*, 1983b) only half of the patients entered the crossover phase.

Potential for selection bias at trial entry

In 16 studies it was claimed that the order of treatment had been randomly allocated but in 14 of these the method of random allocation was not described. Only in the Cambridge study in 1988 (Bradley, *et al.*, 1988) was a secure method of random allocation concealment prior to final trial entry described (third-party involvement). In the 1979 Columbia study (van Stone & Cook, 1978; 1979) a potentially insecure method of

random allocation concealment was described (coin toss with no stated third-party involvement).

Two studies were included on the basis of quasi-randomisation solely because their treatments or treatment periods alternated A–B–A–B (Brezin, *et al.*, 1985; Savidie, *et al.*, 1977). The order of treatments was not randomly allocated. Neither of these studies had data which could be included in any of the meta-analyses; hence, sensitivity analyses to determine the influence of these less methodologically robust studies on the summary statistics could not be undertaken.

Potential for bias in trial analysis

In four of the 18 studies the numbers and reasons for withdrawals and drop-outs were described. One study mentioned that there had been withdrawals but did not give details. A further six studies reported no withdrawals or drop-outs, and seven studies made no mention of withdrawals or drop-outs.

None of the studies from which data were included for meta-analysis had been explicitly undertaken on an intention-to-treat basis.

Potential for bias at time of treatment or outcome assessment

In four studies, patients, healthcare providers and outcomes assessors were explicitly stated to have been blinded. Three studies described an effective method of blinding; the fourth gave no description.

In six studies, no mention was made of blinding. The remaining eight studies, although not always describing the method, mentioned blinding of at least one of three groups: patients, healthcare providers, outcomes assessors. In some studies, healthcare providers and outcomes assessors may have been the same people, and hence our categorisation may have underestimated the degree of blinding.

The quality assessment tool used in this study assumes that the avoidance of bias is best achieved by an RCT with:

- secure concealment of allocation before formal trial entry
- adequate blinding of patients, outcomes assessors and healthcare providers
- descriptions of reasons and numbers of withdrawals and drop-outs
- analysis on an intention-to-treat basis.

None of the trials fulfilled all these criteria.

TABLE 18 Characteristics of included studies: bicarbonate- versus acetate-buffered dialysate in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Antwerp 1983a (de Backer, et al., 1983)	RCT, crossover design; method of randomisation not described; blinding of patients, healthcare providers and outcomes assessors not stated; withdrawals, drop-outs and number lost to follow-up, not stated; possibly intention-to-treat analysis but not clear.	Six patients with terminal renal failure maintained on haemodialysis; sex not stated; age range, 32–71 years; mean weight not stated; co-morbidity: normal ventilatory function as assessed by spirometry and body plethysmography.	Acetate with cuprophane membrane vs. acetate with polyacrylonitril membrane vs. bicarbonate with cuprophane vs. bicarbonate with polyacrylonitril membrane; duration of study, single treatment with each of four combinations; duration of each dialysis, 4 hours; blood flow rate, 250 ml/min; dialysate flow rate, not stated; membrane type, Cuprophane or PAN as above, surface area, 1 m ² ; dialysate sodium and buffer concentrations not stated.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability not stated; arterial blood gases and acid–base balance, pH, PO ₂ , PCO ₂ , at 0, 15, 30, 60 and 240 minutes from start of dialysis; renal bone disease indicators not stated; lipid profile not stated; other parameters: O ₂ uptake, CO ₂ output, respiratory quotient, minute ventilation, tidal volume, inspiratory time and alveolar-arterial oxygen tension difference.	Four comparisons were made in this study; data for each membrane type analysed separately; cuprophane membranes analysed here; for polyacrylonitril membrane see Antwerp 1983b.
Antwerp 1983b (de Backer, et al., 1983)	see Antwerp 1983a.	see Antwerp 1983a.	see Antwerp 1983a.	see Antwerp 1983a.	see Antwerp 1983a; polyacrylonitril membranes only analysed here.
Bologna 1989 (Spongano, et al., 1989)	RCT, crossover design; no description of method of randomisation; blinding of patients, healthcare providers and outcomes assessors, not stated; withdrawals, drop-outs and number lost to follow-up, none; analysis on intention-to-treat basis.	Five patients on haemodialysis; sex, mean age, and mean weight, not stated; co-morbidity, not stated.	Acetate vs. bicarbonate dialysis (vs. acetate-free biofiltration); duration of study, one treatment per dialysate; duration of dialysis, 4 hours; blood and dialysate flow rates not stated; membrane type and surface area not stated; dialysate sodium and buffer concentration not stated.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability: systolic, diastolic and mean arterial blood pressure, heart rate, stroke volume, cardiac output and total peripheral vascular resistance; arterial blood gases and acid balance not stated; renal bone disease indicators and lipid profile not stated.	
Boston 1983 (Schick, et al., 1983)	RCT, crossover design; method of randomisation not stated; blinding of patients and healthcare providers but method not described; blinding of outcomes assessors not mentioned; withdrawals, drop-outs and number lost to follow-up not stated; possibly intention-to-treat analysis but not clear.	Nine stable patients on haemodialysis; M:F, 5:4; mean age, 42.3 years, range, 19–57 years; mean weight not stated; co-morbidity: three had diabetes mellitus as primary renal disease, otherwise only cardiovascular status recorded; at time of study none had congestive cardiac failure, angina or were taking digoxin.	Acetate vs. bicarbonate dialysis; duration of study, two dialyses, 1 week apart; duration of dialysis not stated; blood and dialysate flow rates not stated; membrane type, Gambro 11.5, parallel plate, surface area not stated; dialysate sodium concentration: acetate 130 mmol/l, bicarbonate 139 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 37 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate 4 mmol/l, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability: pulse rate, number of patients experiencing hypotension (decrease in systolic blood pressure > 15 mmHg), ejection fraction, stroke volume, cardiac output and velocity of circumferential fibre shortening; arterial blood gases and acid–base balance not stated; renal bone disease indicators and lipid profile not stated.	

continued

TABLE 18 contd Characteristics of included studies: bicarbonate- versus acetate-buffered dialysate in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Cambridge 1988 (Bradley <i>et al.</i> , 1988)	RCT, crossover design; method of randomisation not stated; blinding of patients and outcomes assessors not stated; healthcare providers not blinded; withdrawals, drop-outs and number lost to follow-up not stated; possibly intention-to-treat analysis but not clear.	Eight patients on haemodialysis; M:F, 5:3; mean age (SD), 52 years (15.6); mean weight not stated; co-morbidity: no evidence of cardiovascular disease, none on any cardiovascular drugs.	Acetate vs. bicarbonate dialysis; duration of study, 4 weeks, one study dialysis session per week, two treatments per dialysate; duration of dialysis, 4 hours; blood and dialysate flow rates not stated; membrane type, hollow fibre, surface area, 1.3 m ² ; dialysate sodium concentration: acetate, 130 mmol/l, bicarbonate, 138 mmol/l; dialysate buffer concentration: acetate dialysate – acetate 35 mmol/l, bicarbonate nil; bicarbonate dialysate – acetate 3 mmol/l, bicarbonate 32 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability: predialysis and change during dialysis in mean arterial pressure, forearm venous tone, forearm vascular resistance and pulse rate; arterial blood gases and acid–base balance: change in bicarbonate concentration during dialysis treatment; renal bone disease indicators and lipid profile not stated.	
Chicago 1990a (Dalal, <i>et al.</i> , 1990)	RCT, crossover design, method of randomisation not stated; patients and healthcare providers blinded but no description, outcomes assessors blinding not stated; withdrawals, drop-outs and number lost to follow-up not stated; possibly intention-to-treat analysis but not clear.	Ten chronic patients on haemodialysis, no known cardiovascular instability or acetate intolerance to normal efficiency haemodialysis; M:F, 10:0; mean age 50 years; mean weight 70 kg; no other co-morbidity stated.	L-lactate vs. acetate vs. bicarbonate dialysis (only acetate vs. bicarbonate comparisons used here); duration of study, single treatment with each dialysate buffer; duration of dialysis, 225 minutes; blood flow rate, 300–500 ml/min; dialysate flow rate, 700 ml/min; membrane type, Baxter CA 210TM, surface area not stated; dialysate sodium concentration 139 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 39 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate 4 mmol/l, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability: systolic, diastolic and mean arterial blood pressure, cardiac output (measured by impedance plethysmography) and total peripheral vascular resistance; arterial blood gases and acid–base balance not stated; renal bone disease indicators and lipid profile not stated.	This is study A in this paper; for study B see Chicago 1990b below.
Chicago 1990b (Dalal, <i>et al.</i> , 1990)	see Chicago 1990a above.	12 patients on chronic haemodialysis; M:F, at least 8 M; mean age and weight not stated; co-morbidity not stated.	Comparisons as Chicago 1990a; duration of study, 2 week run-in using bicarbonate, then 3 weeks on each of three buffers; three dialysis sessions per week, duration 180 minutes; blood flow rate, body weight × 5 ml/min; dialysate flow rate, 800 ml/min; membrane type, Baxter CA 210 TM, surface area not stated; dialysate sodium concentration 139 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 39 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate 4 mmol/l, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms: number of treatments with headaches, nausea or vomiting, weakness or washed-out feeling, muscle cramps; 'dizziness/hypotension' was symptom category in preliminary study but change to 'hypotension severe enough to warrant a treatment intervention'; number of treatments with any of above symptoms stated; intradialytic cardiovascular stability, mean change in systolic, diastolic and mean arterial blood pressure; arterial blood gases and acid–base balance: pH, PO ₂ , PCO ₂ , standard bicarbonate, predialysis levels and change during dialysis recorded for single treatment only; renal bone disease indicators and lipid profile not stated; other outcomes: change in serum phosphate during single treatment; measure of dialysis adequacy, Kt/V.	Preliminary results published in Dalal, <i>et al.</i> , 1989; full study published as study B in Dalal, <i>et al.</i> , 1990.

continued

TABLE 18 contd Characteristics of included studies: bicarbonate- versus acetate-buffered dialysate in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Columbia 1979 (van Stone & Cook, 1978; 1979)	RCT, crossover design; random allocation by coin toss; patients, healthcare providers and outcomes assessors all blinded and method likely to be effective; withdrawals, drop-outs and number lost to follow-up not stated; possibly intention-to-treat analysis but not clear.	Nine stable haemodialysis patients with no known previous acetate intolerance; M:F not stated; mean age and weight not stated; co-morbidity not stated.	Acetate vs. bicarbonate dialysis; duration of study, six treatments on both dialysates, duration of dialysis, 4 hours; blood and dialysate flow rates not stated; membrane type: Travenol 1500, surface area 1.5 m ² – five patients; Cordis model V, surface area 2.5 m ² – four patients; dialysate sodium concentration, acetate 135.4 mmol/l, bicarbonate 133.7 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 37.2 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 35.3 mmol/l.	Intra- and postdialytic symptoms, percentage of treatments with any 'untoward' symptoms and percentage with severe 'untoward' symptoms – specific symptoms not stated; intradialytic cardiovascular stability: systolic and diastolic blood pressure predialysis (supine), lowest intra- and postdialysis (supine and upright); arterial blood gases and acid–base balance: arterial pH, PO ₂ , PCO ₂ after 1 and 2 hours of dialysis; venous bicarbonate and anion gap pre-, after 1 hour, and postdialysis; renal bone disease indicators and lipid profile not stated; other parameters, serum potassium pre-, after 1 hour, and postdialysis.	First published 1978; 1979 version includes extra data relating to blood pressure and serum potassium.
Hamilton 1983a (Shimizu, et al., 1983)	RCT, crossover design, method of randomisation not described but stated to be such as to ensure each dialysate was followed by every other, including itself; patients, healthcare providers and outcomes assessors all blinded and method likely to be effective; numbers and reasons stated for withdrawals, drop-outs and number lost to follow-up – four died, one changed dialysis modality, one transferred to another unit; no intention-to-treat analysis.	34 clinically stable hospital haemodialysis patients; age over 16 years; data on 28 patients analysed; M:F not stated; mean age and weight not stated; co-morbidity not stated.	Acetate with high sodium vs. bicarbonate with high sodium vs. acetate with low sodium vs. bicarbonate with low sodium; duration of study, 36 weeks in 2-week blocks, duration of dialysis, 4–6 hours; blood and dialysate flow rates not stated; membrane type and surface area not stated; dialysate sodium concentration: high, 142 mmol/l, low, 135 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 40 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms: percentage of treatments in which headaches, vomiting, muscle cramps, and non-specific intolerance occurred with any severity or moderate/severe; intradialytic cardiovascular stability not stated; arterial blood gases and acid–base balance not stated; renal bone disease indicators and lipid profile not stated.	Study had four interventions; rather than combining the high and low sodium outcomes, the data are reported separately as published. Hamilton 1983a considers only low sodium dialysate. For high sodium dialysate see Hamilton 1983b.
Hamilton 1983b (Shimizu, et al., 1983)	See Hamilton 1983a above.	See Hamilton 1983a above.	See Hamilton 1983a above.	See Hamilton 1983a above.	Considers only high sodium dialysate; for low sodium dialysate see Hamilton 1983a.
Madras 1991 (Gurudev, et al., 1991)	RCT, crossover design, randomisation method not stated; patients, healthcare providers and outcomes assessors all blinded, method likely to be effective; withdrawals, drop-outs and number lost to follow-up not stated; possibly intention-to-treat analysis but not clear.	30 stable ESRD patients on haemodialysis for > 4 weeks; all on renal transplant list; M:F, 25:5; mean age (SD), 35.62 (11.75); mean weight not stated; co-morbidity, all with hypertension, two with diabetic nephropathy.	Acetate vs. bicarbonate dialysis; duration of study, three treatments with each dialysate buffer, duration of dialysis 300 minutes; blood flow rate, 200 ml/min; dialysate flow rate, 500 ml/min; membrane type, cuprophane, surface area 0.8 m ² ; dialysate sodium concentration, 138 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 40 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 39 mmol/l.	Intra- and postdialytic symptoms – number of treatments associated with and number of patients developing headache, giddiness, nausea/vomiting, malaise, muscle cramps, or symptomatic hypotension; intradialytic cardiovascular stability: supine and standing mean arterial blood pressure before and at 30, 60, 120 and 300 minutes during dialysis; arterial blood gases and acid–base balance: pH, PO ₂ , PCO ₂ , and standard bicarbonate at 0, 30, 60, 120, 300 minutes; renal bone disease indicators and lipid profile not stated.	

continued

TABLE 18 contd Characteristics of included studies: bicarbonate- versus acetate-buffered dialysate in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Newcastle 1983 (Ramos, et al., 1983)	RCT, crossover design, randomisation method not described; blinding of patients, healthcare providers and outcomes assessors not stated; withdrawals, drop-outs and number lost to follow-up not stated; possibly intention-to-treat analysis but not clear.	11 patients maintained on dialysis; M:F, 6:5; mean age 45.7 years, range 31–35 years; mean weight not stated; co-morbidity not stated.	Acetate vs. bicarbonate dialysis; duration of study, 3 weeks, buffer alternating each week, duration of dialysis 4 hours; blood and dialysate flow rates not stated; membrane type, Triex 1, surface area not stated; dialysate sodium concentration 136 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 40 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability not stated; arterial blood gases and acid–base balance: pH, PO ₂ , PCO ₂ pre- and each hour during dialysis for first treatment each week, predialysis only for second treatment each week; renal bone disease indicators: serum ionised calcium, total calcium, inorganic phosphate, parathyroid hormone, (c-terminal by radio-immuno assay) pre- and hourly during dialysis for first treatment each week, predialysis only for second treatment each week; lipid profile not stated.	
Odense 1990 (Otte, et al., 1990)	RCT, crossover design, randomisation method not stated; patients and healthcare providers blinded, likely to be effective; outcome assessors, blinding not stated; numbers and reasons stated for withdrawals, drop-outs and number lost to follow-up – one patient died after treatment allocation but before study commenced from complications following fractured femur; allocated group not stated; analysis not on intention-to-treat basis.	16 stable ESRD patients on regular haemodialysis, none being due to change dialysis mode nor were on renal transplant waiting list; M:F, 10:6; mean age 52.1 years, range 24–74 years; mean weight not stated; co-morbidity, no known malignant disease.	Acetate vs. bicarbonate dialysis; duration of study 6 months, 3 months on acetate and 3 months on bicarbonate dialysis, duration of dialysis, 3–4 hours three times weekly; blood flow rate 200–250 ml/min; dialysate flow rate 500 ml/min; membrane types, Fresenius 40, Fresenius 50 and Biospal 2400, surface area, 0.65–1.0 m ² ; dialysate sodium concentration 140 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 35 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate 3.0 mmol/l, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms: subjective well-being questionnaire (included questions on sleep disturbance, joint pain, dyspnoea, nausea/vomiting, headaches, tiredness, cramps, angina, pruritus, abdominal pain – each complaint scored as 1 point); cramp incidents per patient in 12 weeks; intradialytic cardiovascular stability: hypotensive episodes per patient per 12 weeks (hypotension not defined); arterial blood gases and acid–base balance: predialysis pH, PO ₂ , PCO ₂ , standard bicarbonate and base excess at 0, 4, 8 and 12 weeks; renal bone disease indicators and lipid profile not stated; other outcomes: predialysis serum potassium, urea, sodium, creatinine and haematocrit at 0, 4, 8 and 12 weeks; anthropometric data: weight change (not clear if pre- or postdialysis), skinfold thickness, mid-arm muscle circumference at 0, 12 and 24 weeks; dietary assessment, average energy intake; pre- and postdialysis serum albumin and transferrin levels; therapeutic interventions (hypertonic saline, analgesics, muscle relaxants plus others not described) per patient per 12 weeks.	

continued

TABLE 18 contd Characteristics of included studies: bicarbonate- versus acetate-buffered dialysate in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Ovideo 1986 (Peces Serrano, et al., 1986)	RCT, crossover design; randomisation method not described; blinding of patients, healthcare providers and outcomes assessors not stated; withdrawals, drop-outs and number lost to follow-up not stated; possibly intention-to-treat analysis but not clear.	14 patients maintained on haemodialysis, in two groups – group 1, six patients with known chronic pulmonary disease; group 2, eight patients without signs or symptoms of pulmonary disease and with normal spirometry; M:F, group 1, 3:3, group 2, 6:2; mean age group 1, 54.8 years (range 45–65 years), group 2, 56.7 years (range not stated); mean weight not stated; co-morbidity: groups defined in relation to pulmonary co-morbidity, nothing else stated.	Acetate vs. bicarbonate dialysis; order of dialysate type in each group randomly allocated; acetate dialysis with nasal oxygen also studied but allocation method not stated; duration of study, single treatment with each buffer plus one with acetate plus nasal oxygen; duration of dialysis 4 hours three times weekly; blood flow rate 250 ml/min; dialysate flow rate 500 ml/min; membrane type, cuprophane, surface area 1.0 m ² ; dialysate sodium concentration: acetate 134 mmol/l, bicarbonate 136.5 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 36 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 34.5 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability: mean arterial blood pressure stated as stable with all treatments but no data given; arterial blood gases and acid–base balance: pH, PO ₂ , PCO ₂ , HCO ₃ , at 0, 15, 30, 60 and 120 minutes; renal bone disease indicators and lipid profile not stated.	
Oxford 1991 (Akanji, et al., 1991)	RCT, crossover design; randomisation method not described; blinding of patients, healthcare providers and outcomes assessors not stated; numbers and reasons for withdrawals, drop-outs and numbers lost to follow-up given: eight drop-outs in total but treatment group not specified; analysis not on intention-to-treat basis.	Ten established ESRD patients on regular haemodialysis for > 6 months; five had diabetes with diabetic nephropathy, 5 not diabetic but with chronic glomerulo-nephritis; stable glycaemic control, no hypoglycaemia or hypotension on glucose-free dialysis; M:F, 10:0; mean age (SD): diabetes group 53.0 years (6.6); non-diabetes group 50.0 years (13.0); mean weight – given as body mass index – (SD): diabetes group 23.0 kg/m ² (1.3), non-diabetes group 24.5 kg/m ² (3.7); no other co-morbidity stated.	Acetate vs. bicarbonate dialysis; duration of study, single treatment with each buffer 1 week apart, duration of dialysis, 300 minutes; blood flow rate, 200 ml/min; dialysate flow rate, 500 ml/min; membrane type, Allegro hollow fibre, surface area not stated; dialysate sodium concentration, 131 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 38 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate 2 mmol/l, bicarbonate 30 mmol/l; other interventions: overnight fast and intravenous glucose tolerance test during dialysis treatment.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability not stated; arterial blood gases and acid–base balance not stated; renal bone disease indicators and lipid profile not stated; other outcomes: blood glucose, insulin, lactate, pyruvate, acetoacetate, 3-hydroxy-butyrate, non-esterified fatty acids, glycerol and acetate measured before dialysis, 1 hour after dialysis started and during the i.v. glucose tolerance test.	
Paris 1983 (Lefebvre, et al., 1983)	RCT, randomisation method not described; patients randomised either to stay on acetate dialysis for duration of trial or to switch to bicarbonate dialysis after 90 days; the group that switched thus constituted a separate crossover trial but allocation to treatment order was not randomised; blinding of patients and healthcare providers not stated, outcomes assessors blinded and method likely to be effective; withdrawals, drop-outs and numbers lost to follow-up – stated to be withdrawals but numbers and reasons not stated; analysis not on intention-to-treat basis.	50 patients on outpatient haemodialysis with previous reasonable tolerance of acetate dialysis; M:F, 29:21; mean age (SD) 43 years (13); mean weight (SD), predialysis, day 0: group A, 63.4 kg (1.0), group B 63.4 kg (2.5); co-morbidity, no important co-morbid illness (in particular, vasculopathy, coronary disease, severe hypertension and cardiac dysrhythmia).	25 patients (group A) on acetate dialysis throughout study, 25 patients (group B) allocated to cross over to bicarbonate dialysis after 90 days; duration of study: group A, 18 months, group B, acetate dialysis 3 months, bicarbonate dialysis 15 months; dialysis duration not stated; blood and dialysate flow rates not stated; membrane type and surface area not stated; dialysate sodium concentration, 140 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 38 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability: predialysis supine systolic blood pressure, heart rate, pre-ejection period, left ventricular ejection time, electro-mechanical interval; arterial blood gases and acid–base balance not stated; renal bone disease indicators: predialysis serum calcium and phosphate on days 0 and 540 (mmol/l); lipid profile not stated; other outcomes, predialysis serum potassium on days 0 and 540.	

continued

TABLE 18 contd Characteristics of included studies: bicarbonate- versus acetate-buffered dialysate in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Philadelphia 1985 (Brezin, et al., 1985)	Crossover trial with alternation, method of allocation to first treatment not stated; blinding of patients and healthcare providers stated but not described, outcomes assessors blinding not stated; withdrawals, drop-outs and number lost to follow-up not stated; analysis possibly on intention-to-treat basis but not clear.	105 patients at an outpatient haemodialysis unit; M:F not stated; mean age and mean weight not stated; co-morbidity not stated.	Acetate vs. bicarbonate dialysis, duration of study, 8 weeks divided into four 2-week periods (4 weeks on each dialysate), duration of dialysis not stated; blood and dialysate flow rates not stated; membrane type and surface area not stated; dialysate sodium concentration: acetate 136 mmol/l, bicarbonate 135 mmol/l; dialysate buffer concentration: acetate dialysis – acetate 37.75 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 36 mmol/l.	Intra- and postdialytic symptoms: episodes of 'shock' (presumed to be symptomatic hypotension), vomiting, headaches, muscle cramps; intradialytic cardiovascular stability: initial, lowest and end-dialysis systolic blood pressure; saline requirements also recorded; arterial blood gases and acid-base balance not stated; renal bone disease indicators and lipid profile not stated.	Data from abstract of a presentation only; authors being contacted to ascertain if full study subsequently published.
Seattle 1982 (Pagel, et al., 1982)	RCT, crossover design; randomisation method not stated; patients blinded but method not described, no mention of blinding of healthcare providers and outcomes assessors; numbers and reasons given for withdrawals, drop-outs and numbers lost to follow-up; two patients who participated but were on antihypertensive therapy did not have their data analysed; analysis not on intention-to-treat basis.	21 stable maintenance haemodialysis patients; M:F 9:14; mean age (SD) 54 years (14), range 28–75 years; mean weight (SD): symptomatic group 62.1 kg (8.1), asymptomatic group 62.2 kg (1.7); co-morbidity: no respiratory, cardiac or diabetic history – exclusion criteria: as for co-morbidity.	Acetate (38 mmol/l) vs. bicarbonate (35 mmol/l) vs. acetate (38 mmol/l) plus bicarbonate (10 mmol/l) dialysis; duration of study: single dialysis treatment on each dialysate, three treatments total; dialysis duration 4 hours; blood flow rate 200 ml/min; dialysate flow rate 500 ml/min; membrane type C-DAK (Cordis-Low), surface area 1.8 m ² ; dialysate sodium concentration 140 mmol/l; dialysate buffer concentration: acetate dialysis – 38 mmol/l, bicarbonate nil; bicarbonate dialysis – acetate nil, bicarbonate 35 mmol/l; combination dialysis – acetate 38 mmol/l, bicarbonate 10 mmol/l.	Intra- and postdialytic symptoms: episodes of nausea, vomiting, headache; choice reaction time (time taken to make decision about flashing colour panel, used as objective measure of ability to maintain sustained concentration and hypothesised to relate to 'feelings of well-being') measured pre- and postdialysis; intradialytic cardiovascular stability: predialysis and lowest intradialytic systolic, diastolic and mean arterial blood pressure, change in mean arterial blood pressure (predialysis minus lowest level); arterial blood gases and acid-base balance: pH, plasma bicarbonate and serum acetate change during dialysis; renal bone disease indicators and lipid profile not stated.	Combination buffer data from this study is not included in this review.
Sydney 1977 (Savidie, et al., 1977)	Crossover trial with alternation; allocation to first treatment not randomised; blinding of patients, healthcare providers and outcomes assessors not stated; withdrawals, drop-outs and number lost to follow-up not stated, but all eight patients in results section; analysis on intention-to-treat basis.	Eight patients with ESRD established on haemodialysis with fasting hypertriglyceridaemia on two consecutive occasions (> 150 mg%); M:F 1:7; mean age 44 years, range 29–55 years; mean weight (SD) 60.7 kg (4.7) at first acetate dialysis; co-morbidity: no diabetic or nephrotic patients; no patient had medical or technical complications likely to affect health or dialysis within the ensuing 3 months.	Acetate vs. bicarbonate dialysis; duration of study 12–20 weeks (four periods of 3–5 weeks), duration of dialysis 6 hours; blood flow rate not stated; dialysate flow rate 500 ml/min; membrane type, Cordis-Dow (seven patients), surface area 1.3 m ² ; Gambro optima – one patient; dialysate sodium concentration not stated; dialysate buffer concentration: acetate dialysate – acetate 40 mmol/l, bicarbonate nil; bicarbonate dialysate – acetate nil, bicarbonate 40 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability not stated; arterial blood gases and acid-base balance: pH and standard bicarbonate; renal bone disease indicators not stated; lipid profile: total fasting predialysis plasma cholesterol and triglyceride concentrations; other indicators: mean predialysis urea, relative weight and calorie intake.	

continued

TABLE 18 contd Characteristics of included studies: bicarbonate- versus acetate-buffered dialysate in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Torrance 1981 (Dolan, <i>et al.</i> , 1981; Davidson, <i>et al.</i> , 1982)	RCT, crossover design, method of random allocation not described; patients blinded but method not given; blinding of healthcare providers and outcomes assessors not stated; withdrawals, drop-outs and number lost to follow-up not stated; analysis possibly on intention-to-treat basis but not clear.	Seven routine haemodialysis patients; M:F, 3:4; mean age 44.7 years, range 22–55 years; mean weight 61.2 kg, range 41.0–92.8 kg; co-morbidity: free of cardiovascular and pulmonary disease apart from mild controlled hypertension; two patients with diabetes mellitus as cause of renal failure.	Acetate vs. bicarbonate dialysis; duration of study, one treatment with each dialysate, duration of dialysis, 4 hours; blood flow rate 200 ± 20 ml/min; dialysate flow rate 500 ± 50 ml/min; membrane type, Travenol CF 1500, surface area 1.5 m ² ; dialysate sodium concentration; acetate 130 mmol/l, bicarbonate 130 mmol/l; dialysate buffer concentration: acetate dialysate – acetate 35 mmol/l, bicarbonate nil; bicarbonate dialysate – acetate nil, bicarbonate 35 mmol/l.	Intra- and postdialytic symptoms not stated; intradialytic cardiovascular stability not stated; arterial blood gases and acid–base balance: PO ₂ , PCO ₂ ; renal bone disease indicators and lipid profile not stated; other parameters: VO ₂ (oxygen uptake), VCO ₂ (CO ₂ excretion), VCO ₂ /VO ₂ (respiratory gas exchange ratio).	

Results

The meta-analyses of the results of these studies are presented in *Table 19* (A and B).

Intradialytic symptoms

Five symptom categories were considered.

Headaches

Five studies compared the number of haemodialysis treatments during which headaches were reported. In the 1983 Hamilton trial (Shimizu, *et al.*, 1983), buffers were compared at two levels of dialysate sodium concentrations (high and low) and, hence, was considered as two separate studies in subsequent analyses. The incidence of headaches on bicarbonate dialysis was lower in four of the five trials with an overall estimate favouring bicarbonate dialysis (OR, 0.84; 95% CI, 0.71, 0.99; NNT, 33). Although there was evidence of heterogeneity across the trials (chi-squared test, $2p < 0.05$), over 90% of the data came from the 1983 Hamilton trial and the summary OR is largely determined by this trial.

The 1985 Philadelphia trial reported the incidence of headaches (Brezin, *et al.*, 1985) but in relation to episodes over a period and, hence, could not be included in this meta-analysis. There was a non-significant tendency favouring bicarbonate dialysate.

Nausea and vomiting

In five studies the number of haemodialysis treatments were compared for which nausea and/or vomiting were reported. The estimate of the overall effect favoured the use of bicarbonate (OR, 0.42; 95% CI, 0.26, 0.66; NNT, 49). The results of the

trials were significantly heterogeneous (chi squared test, $2p < 0.01$). The incidence rates of nausea and vomiting in the acetate groups were higher in the three smaller studies, in which there were fewer episodes during bicarbonate dialysis, than in the 1983 Hamilton trial (Shimizu, *et al.*, 1983a; b) in which there was no difference between the groups.

In the 1985 Philadelphia trial (Brezin, *et al.*, 1985), which was not included in the meta-analysis (see above), there were fewer episodes of vomiting in the bicarbonate group (6 versus 30; $p < 0.005$).

Muscle cramps

Data describing muscle cramps were available for only the two parts of the Hamilton trial (Shimizu, *et al.*, 1983a; b) and the smaller Chicago trial (Dalal, *et al.*, 1990b; c). The comparison is therefore dominated by the data from the Hamilton trial, which suggested there was no difference.

The 1991 Madras trial (Gurudev, *et al.*, 1991) was not included in the meta-analysis because no muscle cramps were reported with either dialysate (0/90 treatments with bicarbonate; 0/90 treatments with acetate); hence, no OR could be calculated.

Symptomatic or treatment-requiring hypotension

Two studies with a total of 396 haemodialysis treatments were included in the meta-analysis. The suggestion of a significant reduction in symptomatic hypotension with bicarbonate dialysate (OR, 0.28; 95% CI, 0.11, 0.69; NNT, 17) reflects the findings of the 1979 Chicago trial (Dalal, *et al.*, 1979b; c).

Data from a number of the included studies could not be included in this meta-analysis. In the Odense trial (Otte, *et al.*, 1990), the number of hypotensive episodes (not further defined) per patient over 12 weeks were given. There was no significant difference between the dialysates: bicarbonate, 3.0

(standard deviation, 4.26); acetate, 1.5 (standard deviation, 2.71). Episodes of shock (not further defined) were reported in the Philadelphia study (Brezin, *et al.*, 1985); however, there was no significant difference in the results: bicarbonate, 8; acetate, 19. There was no significant difference in the

TABLE 19A Bicarbonate versus acetate-buffered haemodialysis: overall summary

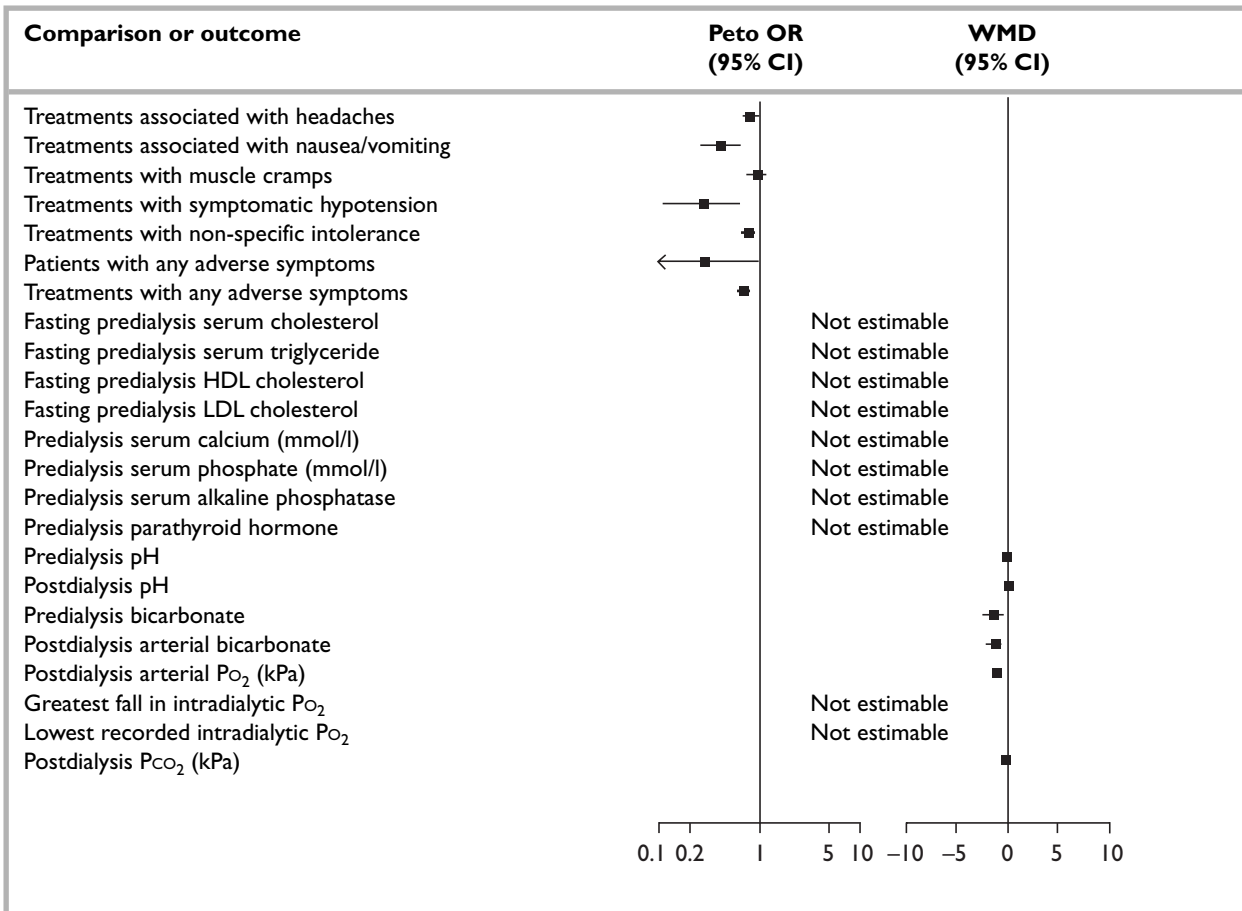
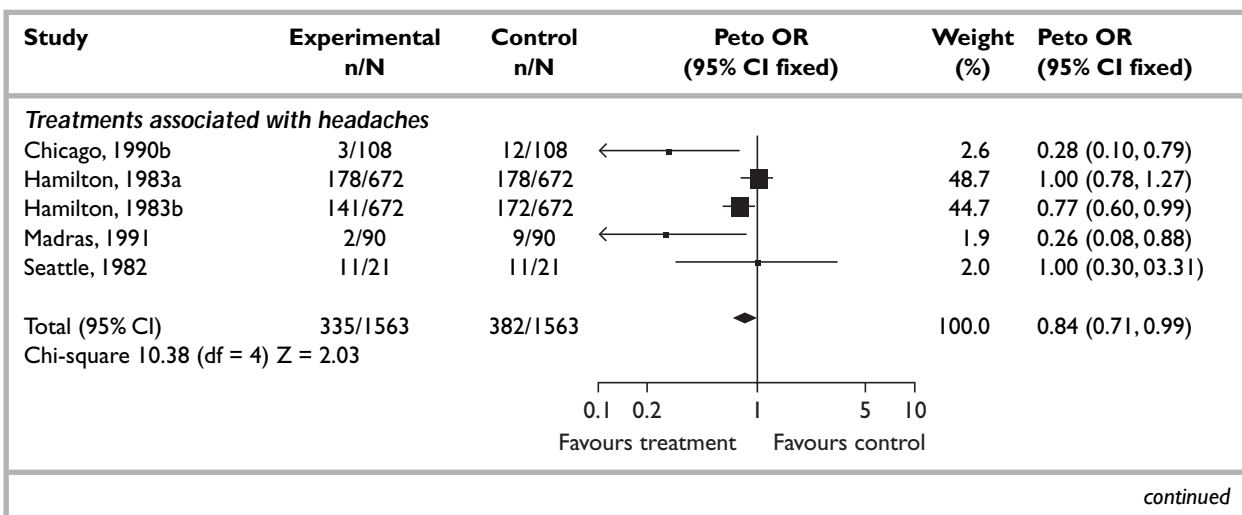


TABLE 19B Bicarbonate versus acetate-buffered haemodialysis: detailed meta-analysis



continued

TABLE 19B contd Bicarbonate versus acetate-buffered haemodialysis: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Treatments with nausea/vomiting					
Chicago, 1990b	1/108	17/108		22.7	0.15 (0.06, 0.38)
Hamilton, 1983a	9/672	11/672		27.0	0.82 (0.34, 1.97)
Hamilton, 1983b	10/672	8/672		24.3	1.25 (0.49, 3.17)
Madras, 1991	2/90	8/90		13.0	0.28 (0.08, 1.01)
Seattle, 1982	2/21	12/21		13.1	0.12 (0.03, 0.44)
Total (95% CI)	24/1563	56/1563		100.0	0.42 (0.26, 0.66)
Chi-square 16.12 (df = 4) Z = 3.74					
0.1 0.2 1 5 10 Favours treatment Favours control					
Treatments with muscle cramps					
Chicago, 1990b	5/108	16/108		6.5	0.32 (0.13, 0.77)
Hamilton, 1983a	108/672	88/672		57.6	1.27 (0.94, 1.72)
Hamilton, 1983b	50/672	64/672		35.9	0.76 (0.52, 1.12)
Total (95% CI)	163/1452	168/1452		100.0	0.97 (0.77, 1.22)
Chi-square 10.53 (df = 2) Z = 0.29					
0.1 0.2 1 5 10 Favours treatment Favours control					
Treatments with symptomatic hypotension					
Chicago, 1990b	2/108	15/108		84.1	0.19 (0.07, 0.51)
Madras, 1991	2/90	1/90		15.9	1.96 (0.20, 19.11)
Total (95% CI)	4/198	16/198		100.0	0.28 (0.11, 0.69)
Chi-square 3.38 (df = 1) Z = 2.77					
0.01 0.1 1 10 100 Favours treatment Favours control					
Treatments with non-specific intolerance					
Chicago, 1990b	2/108	30/108		4.6	0.13 (0.06, 0.27)
Hamilton, 1983a	199/672	211/672		47.9	0.92 (0.73, 1.16)
Hamilton, 1983b	175/672	190/672		44.7	0.89 (0.70, 1.14)
Madras, 1991	2/90	17/90		2.9	0.17 (0.07, 0.45)
Total (95% CI)	378/1542	448/1542		100.0	0.79 (0.67, 0.93)
Chi-square 34.92 (df = 3) Z = 2.87					
0.1 0.2 1 5 10 Favours treatment Favours control					

continued

TABLE 19B contd Bicarbonate versus acetate-buffered haemodialysis: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)		
Patients with any adverse symptoms							
Madras, 1991	3/30	9/30		100.0	0.29 (0.08, 1.03)		
Total (95% CI)	3/30	9/30		100.0	0.29 (0.08, 1.03)		
Chi-square 0.00 (df = 0) Z = 1.92							
0.01 0.1 1 10 100 Favours treatment Favours control							
Treatments with any adverse symptoms							
Chicago, 1990b	9/108	63/108		6.4	0.11 (0.06, 0.19)		
Columbia, 1979a	12/54	24/54		3.2	0.37 (0.17, 0.82)		
Hamilton, 1983a	307/672	322/672		44.6	0.91 (0.74, 1.13)		
Hamilton, 1983b	255/672	293/672		43.3	0.79 (0.64, 0.98)		
Madras, 1991	5/90	15/90		2.4	0.33 (0.13, 0.83)		
Total (95% CI)	588/1596	717/1596		100.0	0.71 (0.61, 0.82)		
Chi-square 54.94 (df = 4) Z = 4.71							
0.1 0.2 1 5 10 Favours treatment Favours control							
Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Predialysis pH							
Chicago, 1990b	12	-7.39 (0.03)	12	-7.38 (0.03)		73.1	-0.010 (-0.034, 0.014)
Odense, 1990	15	-7.34 (0.06)	15	-7.33 (0.05)		26.9	-0.010 (-0.050, 0.030)
Total (95% CI)	27		27			100.0	-0.010 (-0.031, 0.011)
Chi-square 0.00 (df = 1) Z = 0.96							
-0.5 0 0.5 Favours treatment Favours control							
Postdialysis pH							
Madras, 1991	90	-7.45 (0.03)	90	-7.45 (0.03)		100.0	0.000 (-0.009, 0.009)
Total (95% CI)	90		90			100.0	0.000 (-0.009, 0.009)
Chi-square 0.00 (df = 0) Z = 0.00							
-0.5 0 0.5 Favours treatment Favours control							

continued

TABLE 19B contd Bicarbonate versus acetate-buffered haemodialysis: detailed meta-analysis

Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Predialysis bicarbonate							
Chicago, 1990b	12	-20.40 (2.22)	12	-18.90 (2.07)		40.4	-1.500 (-3.217, 0.217)
Columbia, 1979a	54	-19.00 (7.35)	54	-18.00 (2.94)		26.8	-1.000 (-3.111, 1.111)
Odense, 1990	15	-20.30 (2.97)	15	-18.70 (2.32)		32.8	-1.600 (-3.507, 0.307)
Total (95% CI)	81		81			100.0	-1.399 (-2.491, -0.307)
Chi-square 0.19 (df = 2) Z = 2.51							
Postdialysis arterial bicarbonate							
Columbia, 1979a	54	-23.10 (7.35)	54	-18.30 (6.61)		9.6	-4.800 (-7.437, -2.163)
Madras, 1991	90	-26.75 (2.57)	90	-25.90 (3.28)		90.4	-0.850 (-1.711, 0.011)
Total (95% CI)	144		144			100.0	-1.231 (-2.049, -0.412)
Chi-square 7.79 (df = 1) Z = 2.95							
Postdialysis arterial Po₂ (kPa)							
Antwerp, 1983a	6	-12.60 (1.10)	6	-9.60 (1.80)		5.5	-3.000 (-4.688, -1.312)
Antwerp, 1983b	6	-12.10 (1.20)	6	-11.00 (0.80)		11.9	-1.100 (-2.254, 0.054)
Madras, 1991	90	-12.85 (1.44)	90	-11.99 (1.55)		82.6	-0.860 (-1.297, -0.423)
Total (95% CI)	102		102			100.0	-1.007 (-1.404, -0.610)
Chi-square 5.82 (df = 2) Z = 4.97							
Postdialysis Pco₂ (kPa)							
Madras, 1991	90	-5.04 (0.38)	90	-4.88 (0.42)		100.0	-0.160 (-0.277, -0.043)
Total (95% CI)	90		90			100.0	-0.160 (-0.277, -0.043)
Chi-square 5.82 (df = 2) Z = 4.97							

number of patients who experienced 'transient hypotension' (a drop in systolic blood pressure of > 15 mmHg), as reported in the 1983 Boston trial (Schick, *et al.*, 1983): bicarbonate, 2; acetate, 6.

Non-specific intolerance

In four studies (3084 haemodialysis treatments) there were reports of non-specific intolerance. All four studies found that it was less common with

bicarbonate dialysate (NNT, 22). Again there was marked heterogeneity between the results of the Hamilton trial (Shimizu, *et al.*, 1983a; b), which suggested a modest 10% reduction in the OR, and the two smaller trials, which suggested about an 85% reduction in the OR.

Any adverse symptoms

In five studies (3192 haemodialysis treatments) any adverse symptoms were recorded. The overall estimate favoured bicarbonate (OR, 0.71; 95% CI, 0.61, 0.82; chi-squared test for heterogeneity, $p < 0.001$). The pattern was similar to that for non-specific intolerance: all suggested fewer symptoms associated with bicarbonate, but the estimate of effect was much more modest in the larger Hamilton trial (Shimizu, *et al.*, 1983a; b).

General well-being and patient acceptability

Only two studies reported on general well-being and/or patient acceptability. However, different measurement tools were used in these trials, hence the results could not be combined.

In the 1982 Seattle trial (Pagel, *et al.*, 1982), the 'choice reaction time' immediately postdialysis was used as an indicator of well-being. A significant difference favouring bicarbonate was noted (bicarbonate, 9.1 ms, standard error of the mean (SEM), 37.1; acetate, 29.3 ms, SEM, 38.1; $p < 0.05$).

A 'state of well-being index' was used in the 1979 Columbia trial (van Stone & Cook, 1979a; b) in which patients described how they felt both pre- and postdialysis. Although there was no significant difference predialysis, patients using bicarbonate felt significantly better postdialysis than patients using acetate.

Meta-analyses of the included studies indicated a significant reduction in all adverse symptoms, both collectively and individually (apart from muscle cramps) with bicarbonate dialysis.

Any data from the included studies which were relevant to these outcomes but not possible to include in the meta-analysis either supported the use of bicarbonate or failed to find a significant difference between the dialysates.

Cardiovascular stability

The frequency of symptomatic or treatment-requiring hypotension was the only indicator of cardiovascular stability subjected to meta-analysis. The results are recorded above under intradialytic symptoms.

In other studies, parameters were recorded which were relevant to cardiovascular stability but which were not encompassed by our comparisons. In the Columbia trial (van Stone & Cook, 1979a; b), no significant differences in the means of predialysis, postdialysis and lowest intradialytic supine and upright systolic and diastolic blood pressures were found between the dialysates. In the Seattle trial (Pagel, *et al.*, 1982), the change in mean arterial intradialytic pressure was reported as significantly less and the lowest intradialytic systolic, diastolic and mean arterial blood pressures were reported as significantly greater with bicarbonate dialysis. A significantly decreased rate of fall in mean arterial pressure but no difference in change of venous tone during bicarbonate dialysis was reported in the Cambridge trial (Bradley, *et al.*, 1988). Although a significant increase in heart rate with acetate as opposed to bicarbonate dialysis was reported in the Paris trial (Lefebvre, *et al.*, 1983b), there was no significant difference in the fall of systolic blood pressure with bicarbonate compared with acetate dialysis. A significant increase in heart rate was reported with acetate but not with bicarbonate dialysis in the Boston trial; however, Schick and colleagues (1983) found no significant difference between the two dialysates in changes in systolic, diastolic and mean arterial blood pressure, ejection fraction and cardiac output. Only one of the two studies included in the meta-analysis indicated a reduction in symptomatic hypotension with bicarbonate dialysis. In the studies which assessed cardiovascular stability with parameters other than those used in this comparison, no significant differences were usually found between the dialysates. If any significant difference was found, it always favoured bicarbonate dialysis.

Therefore, no conclusive evidence was found that bicarbonate dialysis improves cardiovascular stability in the haemodialysis of patients with ESRD.

Correction of metabolic acidosis

Postdialysis arterial (from arteriovenous fistula) pH and bicarbonate levels indicate how well a particular dialysate buffer has corrected the metabolic acidosis over the course of treatment. Predialysis pH and bicarbonate levels reflect the chronic acid-base status of the patient, which is likely to have greater long-term pathophysiological significance.

Predialysis pH level (after at least one dialysis on specific dialysate)

Two studies were included in the meta-analysis. There was no significant difference between the dialysates (WMD, 0.01; 95% CI, -0.01, 0.03).

Predialysis bicarbonate level (after at least one dialysis on specific dialysate)

Three studies were included in the meta-analysis. A significant difference was found which favoured bicarbonate (WMD, 1.4; 95% CI, 0.31, 2.49).

Postdialysis pH level

Only one study reported postdialysis pH levels (Gurudev, *et al.*, 1991). There was no difference between the dialysates.

Postdialysis bicarbonate level

Two studies were included in this meta-analysis. Bicarbonate dialysate resulted in higher postdialysis bicarbonate levels (WMD, 1.23; 95% CI, 0.41, 2.05). However, a larger difference was observed in one trial than in the other (chi-squared test, $p < 0.01$).

Summary

Bicarbonate dialysis was associated with only a marginally higher pre- and postdialysis blood bicarbonate level compared with acetate dialysis. There was no difference between the dialysates in relation to arterial pH level.

Arterial blood gases

Some of the adverse symptoms and cardiovascular instability experienced on haemodialysis have been attributed to hypoxia. It has been suggested that acetate dialysate may be associated with more severe hypoxia because of loss of respiratory drive caused by hypocarbia (a consequence of greater loss of carbon dioxide into the dialysate).

Postdialysis P_{O_2}

Three studies were included in the meta-analysis. End-dialysis P_{O_2} was higher with bicarbonate dialysis in all three studies (WMD, 1.01; 95% CI, 0.61, 1.40), although the size of the difference varied between them (chi-squared test, $p < 0.05$).

Lowest intradialytic P_{O_2}

None of the studies reported this outcome.

Postdialysis P_{CO_2}

Only the 1991 Madras study (Gurudev, *et al.*, 1991) reported postdialysis P_{CO_2} ; it was significantly higher at the end of bicarbonate dialysis compared with acetate dialysis (WMD, 0.16; 95% CI, 0.04, 0.28).

Not all data relevant to the stated outcomes from the included trials could be included in the meta-analyses, because of the various time points used by the different studies when reporting acid-base and blood gas data. These data may be summarised as follows.

- In the Chicago trial (Dalal, *et al.*, 1989; 1990b), a significant decrease in P_{O_2} and P_{CO_2} during acetate but not bicarbonate dialysis was reported, together with a significantly faster correction of pH and bicarbonate levels with bicarbonate dialysis. However, by 1 hour postdialysis there were no significant differences in these parameters.
- The 1979 Columbia trial (van Stone & Cook, 1978; 1979) reported significantly higher levels of P_{O_2} , P_{CO_2} , and pH after a 3-hour dialysis with bicarbonate compared with acetate.
- The data from the 1983 Newcastle trial (Ramos, *et al.*, 1983) showed a significant fall in P_{O_2} during acetate dialysis but not during bicarbonate dialysis. The P_{O_2} had returned to predialysis values by the last hour of dialysis, the pH level was raised more rapidly during bicarbonate dialysis, and P_{CO_2} and bicarbonate level were significantly increased during bicarbonate but not during acetate dialysis.
- A significant fall in P_{O_2} during acetate dialysis (still present at end of dialysis) but not during bicarbonate dialysis was reported in the 1981 Torrance trial (Dolan, *et al.*, 1981; Davidson, *et al.*, 1982).
- The results of the 1983 Antwerp trial (de Backer, *et al.*, 1983) demonstrated a significant fall in P_{O_2} with both acetate and bicarbonate dialysate when using cuprophane dialysis membranes but only with acetate dialysate when using polyacrylonitril membranes.
- In the 1982 Seattle trial (Pagel, *et al.*, 1982), significantly higher bicarbonate and pH levels after 1 hour of dialysis, which persisted throughout the dialysis treatment, were reported during bicarbonate dialysis compared with acetate dialysis.

Overview

The meta-analysis and other data from the included studies indicate that bicarbonate dialysis is more likely to avoid dialysis-associated hypoxia than acetate dialysis. However, there was no evidence that this improved either morbidity or mortality.

Fasting lipids

Only the 1977 Sydney trial (Savidie, *et al.*, 1977) reported on fasting lipids. A mean difference could not be calculated, however, because the relevant standard deviation could not be derived from the data published. No significant difference in fasting predialysis lipids between bicarbonate and acetate dialysis was noted.

Indicators of renal bone disease

The 1983 Newcastle trial (Ramos, *et al.*, 1983) was the only one in which data relevant to renal

bone disease was presented but, because these data were only presented graphically, they could not be included in a meta-analysis. However, there was no significant difference between bicarbonate and acetate dialysis relative to predialysis calcium, phosphate and parathyroid hormone levels.

Discussion

Bicarbonate has largely supplanted acetate as the most frequently used dialysate buffer in haemodialysis/haemofiltration. In general, bicarbonate-buffered dialysate is used for 78% of patients on haemodialysis/haemofiltration in the UK and for 76% of patients in Europe (Vallerrabano, *et al.*, 1996). However, some countries such as Bulgaria and Romania have lagged behind this general switch to bicarbonate dialysis. The switch from acetate to bicarbonate haemodialysis was based on perceived advantages in reducing intradialytic symptoms (Leenan, *et al.*, 1980; Heneghan, 1982), improved cardiovascular stability (Okusa, *et al.*, 1982), better correction of metabolic acidosis, superior lipid profile and, possibly, a slowing of the progression of renal bone disease.

This systematic review of the literature has attempted to define whether this switch to bicarbonate-buffered haemodialysis is supported by evidence from good clinical trials, which specific putative benefits are so supported and what the economic outcomes of the change have been.

Meta-analyses of the included studies indicated a significant reduction in all adverse symptoms apart from muscle cramps, both collectively and individually, with bicarbonate dialysis. The NNT (for example, 33 bicarbonate haemodialysis treatments would, on average, need to be undertaken in order to produce one extra treatment without headaches) should be considered in the context of the number of treatments each patient requires each year (approximately 150). However, there was considerable heterogeneity across the studies, although this was related predominantly to magnitude rather than direction of effect. It is difficult to identify precisely the explanation for this heterogeneity across trials; however, much is a consequence of the difference in size of effect favouring bicarbonate noted between the 1983 Hamilton studies (Shimizu, *et al.*, 1983) and the 1991 Madras (Gurudev, *et al.*, 1991) and 1990 Chicago studies (Dalal, *et al.*, 1989; 1990). This may be attributable to differences in the duration of the study (number of treatments per patient) and in the method of symptom reporting. The 1983 Hamilton study assessed approximately 96 dialysis

treatments per patient while the 1991 Madras study assessed six treatments per patient and the 1990 Chicago study only two per patient. The method of adverse symptom reporting in the 1983 Hamilton study (and in the 1982 Seattle study (Pagel, *et al.*, 1982)) was explicitly by patient questionnaire, while the 1991 Madras and 1990 Chicago studies appear to have been recorded by dialysis staff. The reporting of symptoms by dialysis staff might under-record adverse symptoms compared with a patient questionnaire.

The review has generated evidence in support of the use of bicarbonate-buffered haemodialysis in the treatment of all patients with ESRD. However, the evidence only conclusively favours bicarbonate haemodialysis in relation to a reduction in intradialytic symptoms, particularly headaches, nausea and vomiting, and symptomatic hypotension. There is no clear evidence that bicarbonate dialysis has any effect on the frequency of intradialytic muscle cramps, leads to a more favourable lipid profile or slows the progression of renal bone disease; however, there are few data available for these outcomes. The evidence of improved cardiovascular stability is inconclusive. This may be a consequence of our inability to summate various cardiovascular parameters from the different studies. There is evidence of a modest improvement in control of metabolic acidosis with bicarbonate, although the clinical and pathophysiological relevance of this is uncertain.

Early studies suggested that the improvement in outcomes associated with switching to bicarbonate haemodialysis may be particularly marked in certain patient groups, such as those with acute renal failure, cardiovascular instability or known acetate intolerance. None of the studies included exclusively examined these patient groups; indeed, in general, patient groups were composed of chronic stable patients with limited associated co-morbidity. The results of this review may therefore underestimate the beneficial effect of bicarbonate-buffered haemodialysis in respect to these sub-groups.

In the UK at least, bicarbonate haemodialysis is no longer significantly more expensive than acetate haemodialysis. This is a dramatic change from the situation some 5–10 years ago. The initially greater cost of bicarbonate haemodialysis certainly slowed its uptake, even by those convinced of the clinical benefits. The health economics history of bicarbonate haemodialysis may be illustrative of the implementation of high technology advances in general. Initial studies suggested that it had at least a modest superiority over acetate dialysis, which seemed to be most marked in relation to relatively

small patient groups, such as those with cardiac disease or with known acetate intolerance. If bicarbonate dialysis had been restricted to these groups, it is likely that its cost would have remained significantly higher than acetate dialysis. However, its general use in the stable dialysis population has led to a significant fall in cost.

When undertaking this review, a number of methodological problems were encountered which may be relevant to future reviews in this area. The management of ESRD is a low patient volume and high technology speciality; hence, trials have tended to be of small populations. The very high drop-out rates from medium or long duration studies, which are an inevitable consequence of dialysis technique failure, renal transplantation and high morbidity and mortality in this population, may also have encouraged trials of short duration. Studies assessing important, unequivocal primary outcome measures such as death are rare because they require relatively prolonged follow-up. Moreover, primary outcomes such as death cannot be assessed satisfactorily using a crossover study design. Secondary outcome measures are more likely than primary ones to change significantly over the course of a short study. The routine management of dialysis patients produces a vast array of secondary outcome measures, such as blood pressure recordings and biochemical data. These two factors may have influenced, and are likely to continue to influence, the predominance of surrogate endpoints in studies of dialysis treatment. Essentially similar surrogate endpoints may be recorded differently by different studies; reported bicarbonate may, for example, be pre- or post-dialysis, while cardiovascular stability may be assessed by many different parameters, from mean arterial blood pressure to changes in systolic blood pressure. This variation in recording of similar outcomes presented significant difficulties in this review, as data from various trials could often not be combined.

Economic evaluation

Introduction

The principles of economic evaluation are described in detail in chapter 3 (page 9) including, in an economic framework, the manner in which costs and outcome are related (see, in particular, *Table 2* and *Figure 3*).

Aims

Bicarbonate can be used as a buffer in haemodialysis and has been suggested as an alternative to acetate-buffered haemodialysis in the belief that

patients dialysed with bicarbonate suffer fewer complications. The relative efficiency of these two alternatives will be investigated using the framework of economic evaluation outlined in chapter 3. More specifically, the aims of this economic evaluation are:

- (i) to investigate the relative resources used and the cost of acetate and bicarbonate haemodialysis fluids using data extracted from the identified RCTs and non-randomised studies which compared acetate and bicarbonate buffers in haemodialysis
- (ii) to combine data on differences in costs with data on differential benefits to patients from the systematic review of effectiveness above in order to assess the relative efficiency of haemodialysing patients with bicarbonate or acetate buffer.

Methods

Data collection and extraction

The methods used are described in detail in chapter 3 of the main report.

Benefits to patients

The systematic review of RCTs or quasi-RCTs described above had as its main objective the synthesis of data on the effectiveness of haemodialysis with acetate compared with bicarbonate as a buffer from the RCTs. Information was extracted from the RCTs on the following outcomes:

- (i) the frequency of adverse symptoms during dialysis
- (ii) cardiovascular stability during dialysis
- (iii) the patient's lipid profile
- (iv) the progression of renal bone disease.

Identification of resource use and costs

The identification of the relative resources used when dialysing patients with either bicarbonate or acetate haemodialysis involved four steps.

1. The process of care was defined so that all items of resource use could be identified; for example, resources could potentially be consumed during three main stages: preparation of the dialysate; the dialysis session itself; and in the treatment of any complications which may occur.
2. All the relevant information was extracted from the RCTs.
3. The data on resource use contained in the non-randomised studies was assessed.
4. The information on resource use was then combined with information on the unit cost

of the resources to determine the cost differential between bicarbonate and acetate haemodialysis using methodology described below. This differential could then be compared with data on differential benefits to patients obtained from the systematic review of effectiveness.

Model of costs

1. **Dialysate preparation** The bicarbonate dialysate can be prepared in three ways. First, it can be mixed by hand from a pre-prepared powder. Second, the dialysate powder can be automatically mixed by the dialysis machine. Finally, the dialysate solution can be obtained as a premixed concentrate. Acetate dialysate is normally only provided as a pre-mixed concentrate (G Anderson, Gambro: personal communication, 1996). The resources (and costs) required for each of the three bicarbonate options are different; the additional cost of bicarbonate dialysate is, therefore, dependent on the method of preparation of the dialysate. The prices of the alternative forms of preparation of the dialysate were obtained from the manufacturers. Staff costs were estimated from the relevant UK NHS salary scales (NHS, 1996a; b) together with estimates of time required.
2. **The dialysis session** The information extracted from the RCTs indicates that the resources required to perform the dialysis were independent of the nature of the buffer used. The same equipment was used for both dialysates and the sessions were of the same length (de Backer, *et al.*, 1983; Spongono, *et al.*, 1989; Schick, *et al.*, 1983; Bradley, *et al.*, 1988; Dalal, *et al.*, 1989; 1990; van Stone & Cook, 1979; Shimizu, *et al.*, 1983; Gurudev, *et al.*, 1991; Ramos, *et al.*, 1983; Otte, *et al.*, 1990; Peces Serrano, *et al.*, 1986; Akanji & Sacks, 1991; Lefebvre, *et al.*, 1983; Brezin, *et al.*, 1985; Pagel, *et al.*, 1982; Savidie, *et al.*, 1977; Dolan, *et al.*, 1981). Therefore, any difference in the cost of the dialysis is due solely to the different cost of the dialysate used.
3. **Treatment of complications** The cost of treating complications was also calculated. In order to calculate the relative cost of complications associated with the different methods of delivering bicarbonate compared with acetate haemodialysis, the model depicted in *Figure 10* was used. In this analysis it has been assumed that when a particular complication occurs then treatment is always provided. Data from the identified RCTs, which provided the best quality information avail-

able, were extracted on the proportion of patients who had a specific complication such as headache, nausea or muscle cramps. This provided information on the probability that a patient would receive treatment for a complication in a set period (either per session, per week or per month). The review of the economic aspects of the RCTs and non-randomised studies attempted to identify the precise treatment provided for a specific complication.

The treatments were then costed according to the staff time, consumables, overheads and capital that the treatment consumed. The estimates of staff time come from an American paper by Jones and colleagues (1995) which asked a panel of clinicians and nurses to estimate staff time for selected clinical vignettes of complications of haemodialysis (including some of the complications of interest here). It provided upper and lower estimates of staff time, thus allowing calculation of upper and lower estimates of the cost of complications.

The price of any pharmaceuticals consumed was taken from the BNF (BMA, 1996); the cost of staff time was estimated by combining information on time with that from the relevant UK NHS salary scales (NHS, 1996a; b). An important assumption in this type of model is that the probability of having a complication (and therefore, receiving treatment) is independent of the probability of having any other type of complication.

Results

Benefits to patients

The results of the systematic review of effectiveness were reported earlier. In brief, the review studied five symptom categories: headaches, nausea/vomiting, muscle cramps, symptomatic or treatment-requiring hypotension and non-specific intolerance. The meta-analysis showed an overall estimate of the frequency of occurrence of headaches favouring bicarbonate haemodialysis (OR, 0.84; 95% CI, 0.71, 0.99). For nausea and vomiting, the estimate of overall effect favoured the use of bicarbonate haemodialysis (OR, 0.42; 95% CI, 0.26, 0.66). There was no significant difference for muscle cramps (OR, 0.97; 95% CI, 0.77, 1.22). There was a significant reduction in symptomatic hypotension with bicarbonate haemodialysis (OR, 0.28; 95% CI, 0.11, 0.69). For non-specific intolerance, the overall estimate favoured bicarbonate haemodialysis (OR, 0.79; 95% CI, 0.67, 0.93).

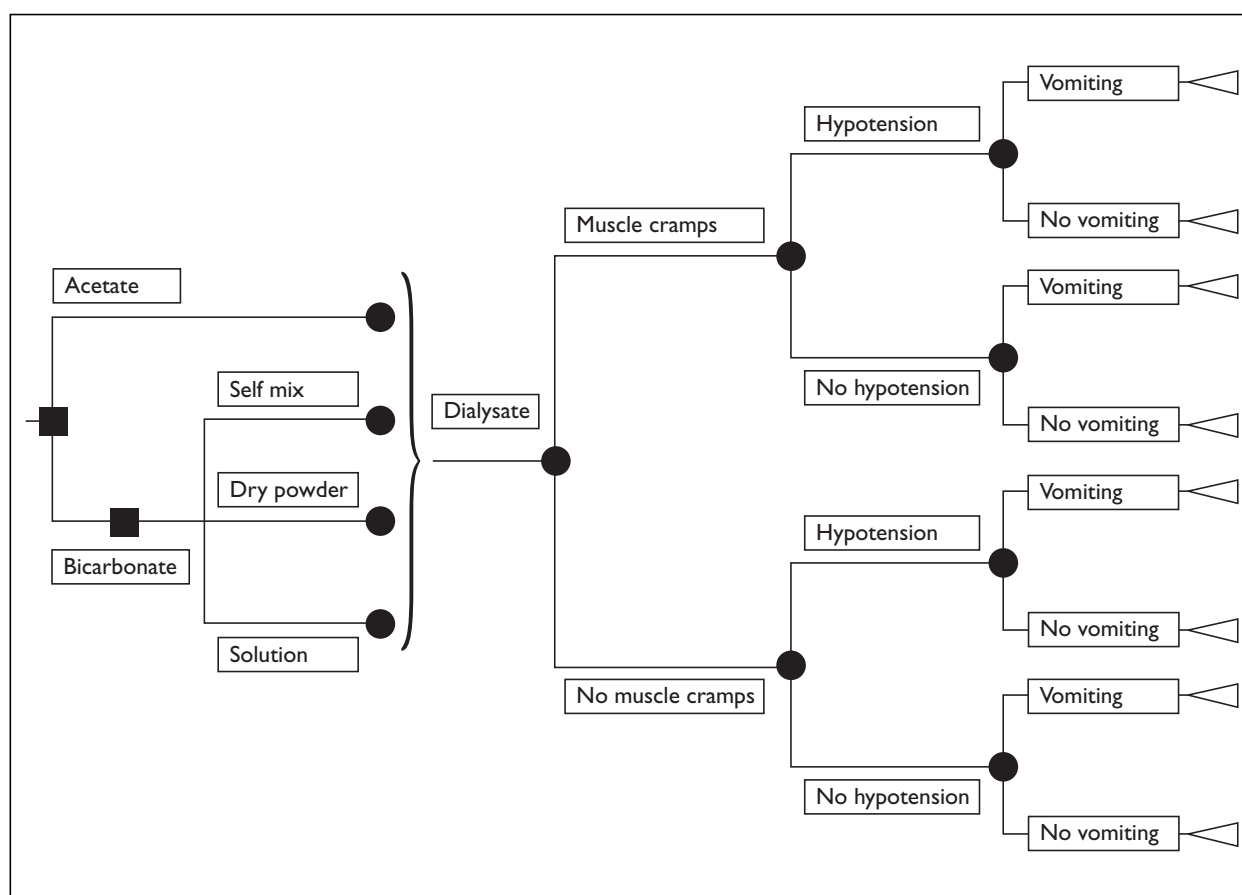


FIGURE 10 Decision model to compare the alternative forms of haemodialysis (■, decision node; ●, chance node; ◁, terminal node)

Two RCTs assessed general well-being and patient satisfaction; they found that patients felt significantly better with bicarbonate dialysis compared with acetate dialysis. No significant differences were found between acetate haemodialysis and bicarbonate haemodialysis when cardiovascular stability, correction of metabolic acidosis, postdialysis pH and bicarbonate, predialysis pH (after at least one dialysis on a specific dialysate) and bicarbonate (after at least one dialysis on a specific dialysate), arterial blood gases, postdialysis P_{O_2} , fasting lipids and indicators of renal bone disease were measured.

The meta-analyses and the other data from the included studies indicate that dialysis-associated hypoxia occurs less frequently when bicarbonate is used as the dialysis buffer. There was no evidence that this improved either morbidity or mortality.

Resource use and costs

None of the studies identified by this review involved any form of economic or cost analysis of bicarbonate haemodialysis compared with acetate haemodialysis. The principle cost differences between the two modes of treatment result from differences in the method of preparation, the

cost of the dialysate used and the cost of treatment of complications.

Resources used before and during the dialysis session

The RCTs provided information on the nature of the dialysates available. To find the cost of preparation of these dialysates, manufacturers were contacted to provide information on the costs of alternative preparations. The differences in cost between acetate and bicarbonate are shown in *Table 20* and were estimated for the following three scenarios:

- each dialysate is in a prepacked solution
- the bicarbonate is mixed from commercially available powder by hand, while the acetate is a prepacked solution that is ready for use
- the bicarbonate comes in a container of dry powder which the dialysis machine apportioned and, again, the acetate comes as a prepacked solution.

Complications

Cost estimates for complications were obtained by combining the staff time estimates with the relevant salary scales and the cost of any consum-

TABLE 20 The cost per patient per session of the alternative forms of dialysate and the different methods available for their preparation

Dialysate	Type	Cost (£ per session)		Preparation (£ per session)	Acid (£ per session)		Total (£ per session)	
		Low	High		Low	High	Low	High
Bicarbonate	Self mix ^{a,b,c}	1.90	2.10	1.05	2.45	3.15	5.40	6.30
Bicarbonate	Dry concentrate ^{a,b}	4.00	5.95		2.45	3.15	6.45	9.10
Bicarbonate	Solution ^{a,b}	4.90	6.30		2.45	3.15	7.35	9.45
Acetate	Solution ^{a,b}	4.90	6.30				4.90	6.30

^a The same dialysis machine can be used for both acetate and bicarbonate haemodialysis
^b 8 litres of dialysate solution is required per patient
^c Mixing of dry powder takes one grade C nurse 1.5 hours to prepare a batch of 100 litres

TABLE 21 The staff costs of complications

Complication	Staff time (hours)		Consumable cost (£)	Combined costs (£)	
	Low	High		Low	High
Muscle cramp	0.083	0.5	0	0.99	3.94
Hypotension	0.083	1.167	2.00	2.99	3.94
Vomiting	0.25	0.75	0.50	3.47	8.86

ables (*Table 21*). The probabilities for the complications which are obtained from the systematic review of effectiveness are shown in *Table 22*. The higher the probability, the more chance there is of that complication occurring. It was not possible to obtain cost estimates for the treatment of headaches or for non-specific intolerance. The significance of this is discussed below.

Using the data contained in *Tables 21* and *22*, the cost of complications can be calculated. This information can then be combined with the cost of dialysates shown in *Table 20*. The results are presented in *Table 23*.

The costs for each of three methods of preparation of bicarbonate buffer and the cost of acetate sup-

TABLE 22 The probabilities of complications for both acetate and bicarbonate per patient per session

Complication	Acetate	Bicarbonate
Muscle cramps	No significant difference	
Hypotension	0.08	0.02
Vomiting	0.035	0.0154

plied in pre-mixed solution are shown in *Table 23*. High, medium and low estimates are provided for the methods of preparation of each form of dialysate. The cost of preparation depends upon estimates of the cost of the buffer, the costs of acid for the bicarbonate and an estimation of the cost of mixing the bicarbonate for the self-mixed bicarbonate. The information on the price of bicarbonate obtained from the manufacturers suggests that bicarbonate is, on average, sold at a substantial discount from the list price. Acetate, however, is sold on average, at a price roughly similar to the list price (G Anderson, Gambro; personal communication, 1996). Therefore, the costs of bicarbonate would tend to be at the lower values while the acetate would tend to be the higher. Likewise, the cost of complications is also split into a high and low estimate. The values highlighted in the two final columns represent the likely cost per session of acetate and bicarbonate. (Note that only those areas where resource use is likely to differ between acetate and bicarbonate have been costed. For example, the same dialysis machines can be used for both dialysates and dialysis sessions take the same time. Therefore, the cost of the dialysis machines is not included in the evaluation).

TABLE 23 The cost per patient per session of using alternative types of dialysate (assuming the same dialysis machine can be used for both types of dialysate)

Dialysate	Type	Preparation (£ per patient per session)		Cost of complications (£ per patient per session)		Total cost (£ per patient per session)	
		Low	High	Low	High	Low	High
Bicarbonate	Self mix	5.40	6.30	0.11	0.22	5.51	6.51
	Dry concentrate	6.45	9.10	0.11	0.22	6.67	9.32
	Pre-prepared	7.35	9.45	0.11	0.22	7.46	9.67
Acetate	Pre-prepared	4.90	6.30	0.36	0.62	5.26	6.92

The cost of acetate and bicarbonate haemodialysis is heavily influenced by the cost of the dialysates themselves. The results presented above show that the episodes of hypotension, nausea and vomiting, and hypotension do decrease when bicarbonate buffer is used in preference to acetate buffer. The overall level of complications with acetate, however, is not high and the reduction in complications due to the use of bicarbonate dialysate is not great. Therefore, even when it is assumed that all episodes of any complication require active treatment, the reduction in cost caused by the reduction in complications requiring treatment is small and does not greatly affect the overall results.

Combining costs and benefits

The combination of the information on the relative effectiveness and cost of acetate and bicarbonate haemodialysis can provide information on the relative efficiency of the two alternatives. The available information suggests that bicarbonate haemodialysis provides more benefits to patients than acetate haemodialysis at the same or lower cost. In terms of the cost–benefit framework described in *Figure 3*, the results suggest that we are in squares A1 or B2, marked ‘Yes’. In both these areas the available evidence suggests that bicarbonate-buffered haemodialysis is more efficient than acetate-buffered haemodialysis.

Discussion

Bicarbonate haemodialysis is no longer significantly more expensive than acetate haemodialysis, at least in the UK. This is a dramatic change from the situation of 5–10 years ago. The greater initial expense of bicarbonate haemodialysis certainly slowed its uptake, even by those convinced of its clinical benefits. There have been no published economic evaluations comparing the use of bicarbonate and acetate buffers. Given the real but apparently quite small benefits of bicarbonate over acetate, an earlier economic

evaluation would have found that bicarbonate would have been more expensive but more beneficial. The effect on cost is illustrated by the results presented in *Table 23*, which indicates that these costs are very sensitive to the costs of the dialysates. Over the last 5 years, use of bicarbonate has increased and the price has fallen, whereas the use of acetate has fallen and its price has remained virtually unchanged. Initial studies suggested that bicarbonate haemodialysis had a modest superiority over acetate dialysis in terms of effectiveness. This superiority seemed to be most marked in relation to relatively small patient groups, such as those with cardiac disease or with known acetate intolerance. If bicarbonate dialysis had been restricted to these groups, it is likely that the cost would have remained significantly higher than those for acetate haemodialysis and, in terms of *Figure 3*, bicarbonate haemodialysis relative to acetate haemodialysis would fall in the shaded area C1. A judgement was implicitly made that the extra benefits provided by bicarbonate haemodialysis relative to acetate haemodialysis were worth the extra cost of bicarbonate. However, its general use in the stable dialysis population has led to a significant drop in its cost, which has changed the relative efficiency and moved bicarbonate haemodialysis to areas A1 or B2, thus indicating that it is more efficient than acetate haemodialysis.

Costs are derived from the estimates of resource use taken from different studies. There are questions as to how generalisable such data could be. The quantity of resources consumed in any given setting are influenced by their prices, which can and do vary between settings. One assumption made, on the evidence from studies from different countries (and, hence, facing very different unit prices) was that the cost of the dialysis session was the same. Thus, any unit price differences in this situation are not relevant. One area, however, where such differences are potentially relevant is in the determination of the cost of treating

complications. Staff time estimates were obtained from one American study. It is conceivable that the time estimates could vary between countries. In the context of this study such variations are unimportant because of the small overall probability of complications requiring treatment per session. A further issue is that it was not possible to gain cost estimates for the treatment of all complications. The incidence of headaches and non-specific intolerance differed between acetate and bicarbonate haemodialysis with the difference favouring bicarbonate. It was not possible to cost the treatment of either headaches or non-specific intolerance but, given the results presented, it is likely that this only strengthens the case for bicarbonate haemodialysis.

Conclusions and implication

Policy implications

1. Bicarbonate dialysis is preferable to acetate dialysis for the haemodialysis of patients with ESRD because of the associated reduction in intra-dialytic adverse symptoms and similar cost.
2. In countries with less well-financed renal replacement services, who continue to depend on haemodialysis machines that can only use acetate-buffered dialysate, replacement of these machines as replacements are required with those that can use either dialysate should be encouraged. However, the cost to a healthcare system of a complete rapid change to new dialysis machines or modification of all their present machines would not be warranted on the basis of the relatively modest benefits which bicarbonate dialysis offers. The benefits of such changes need to be considered in terms of their opportunity cost and this will vary from country to country. The provision of information on the costs and benefits of such a change provided in this study should assist in the estimation of such opportunity costs.

Future research needs

1. Methodologically sound clinical trials with long-term follow-up comparing bicarbonate with acetate haemodialysis are rare. We should continue to be open-minded about the possible beneficial or adverse effects that bicarbonate dialysis may have on long-term outcomes such as lipid profile and cardiovascular disease, renal bone disease and morbidity.
2. A further RCT at this stage is unlikely to produce significantly different data from that which we have already and is therefore unlikely to change clinical practice.

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Appendix 6

Systematic review 3: Comparison of short duration with standard duration haemodialysis treatments for patients with ESRD

Background

Shortening of haemodialysis treatment time is welcomed by the patient and is seen by the health-care purchaser as an improved use of resources. Technological advances coupled with patient pressure and pressure on costs led to the development and implementation of shortened dialysis schedules, particularly in USA, during the late 1970s and early 1980s. However, during the 1980s, the annual mortality rate in patients in the USA began to increase as the average dialysis treatment times decreased (Berger *et al.*, 1991; Held *et al.*, 1990). The trend towards shorter dialysis time was never as pronounced in Europe or Japan, both countries having a significantly lower annual mortality rate in dialysis patients than the USA.

If short dialysis is at least comparable to standard dialysis in terms of clinical outcome, it should be offered to all appropriate patients. If, however, there are significant disadvantages compared with standard dialysis in either the short or long term, then patients to whom it is offered should be made aware of the potential trade-off.

Objectives

The objective of this review is to ascertain whether shortened rather than standard haemodialysis treatment times affect the short- or long-term mortality, morbidity or quality of life of patients with ESRD. It also attempts to assess patient preference and to estimate any impact shortened dialysis times may have on healthcare resource use. The hypotheses being tested are that shortened treatment times are associated with:

- (i) no increase in mortality
- (ii) no increase in morbidity (both intra- and interdialytic)
- (iii) increased patient preference
- (iv) improved quality of life for patients.

Materials and methods

Criteria for considering studies for this review

Types of studies An attempt was made to identify all trials comparing short duration (3.5 hours or less) haemodialysis treatment sessions (experimental group) with standard duration (more than 3.5 hours) sessions (control group) in patients with ESRD maintained on haemodialysis, in which patients were prospectively randomly (for example, sealed envelopes with third party involvement) or quasi-randomly (for example, alternate patients or alternate treatments) allocated to either treatment. Crossover trials in which treatments alternated at least to the degree of A–B–A–B were also included, even if the allocation to first treatment was neither random nor quasi-random.

Types of participants Patients with ESRD maintained on haemodialysis irrespective of age, sex, race, primary renal disease, vascular access or comorbidity. Trials which were exclusively comprised of patients with acute renal failure were excluded. The definition of ESRD by each individual study was accepted.

Types of intervention Patients in the experimental group received short duration haemodialysis treatment sessions of less than 3.5 hours per session while patients in the control group received standard duration haemodialysis treatment sessions of more than 3.5 hours per session. Dialysis was undertaken three times per week in both groups. Within these parameters, the definition of short and standard dialysis time for each individual study was accepted. Any variation in dialysis technique, such as bicarbonate dialysis, high-flux or high-efficiency dialysis membranes, dialysate-sodium modelling and high blood flow rates, were acceptable. However, studies that included haemofiltration or haemodiafiltration treatments were excluded.

Types of outcome measures

1. Mortality (all causes).
2. Intradialytic morbidity – nausea or vomiting,

- headache, muscle cramps, hypotension, non-specific intolerance.
3. Interdialytic morbidity – predialysis hypertension, hospital admission rate for all causes, duration of hospitalisation.
 4. ‘Dialysis adequacy’ as indicated by Kt/V, URR, predialysis blood urea, creatinine, potassium, phosphate and acid–base balance.
 5. Patient acceptability (any scale or measurement accepted).
 6. Quality-of-life assessment (any scale or measurement accepted).

Search strategy for identification of studies

The search strategy used was one developed for the identification of all possible RCTs or quasi-RCTs relating to the management of ESRD, and is described in detail in chapter 2 and appendices 2 and 3.

Methods of the review

Identified studies were evaluated using a study evaluation form and those which met the eligibility criteria (included references) were then considered in detail. Data were extracted using a data abstraction form designed for this review (see appendix 10). Review Manager v. 3.0 was used for the analysis. A full description of the methods used is given in chapter 2.

Description of studies

Only a single study, the National Cooperative Dialysis Study (Lowrie *et al.*, 1983) met the inclusion criteria for this review. The full study was published as a number of separate papers in a single volume of *Kidney International* in 1983. Each individual paper is listed in this review. A preliminary report of the study was published in *New England Journal of Medicine* in 1981 and is also listed although, apart from data on hospitalisation rates, it contains no additional information. The study covered the period 1974–76. A total of 165 patients were randomised, and there were 85 withdrawals during the randomised phase. Patients were randomised to four groups, each determined by its dialysis time (short versus standard) and its dialysis ‘adequacy’ (as defined by its ‘prescribed’ time-averaged concentration of urea – high versus low). A summary of the main features of the study is presented in *Table 24*.

Methodological quality of the included study

The single study was a relatively large, partially balanced, randomised controlled, open, parallel (during randomised phase), multicentre trial undertaken in the USA. Random allocation was

by third party (the data coordinator at the lead centre) using sequentially numbered sealed envelopes. The sequence was generated before initiating the study with the intention of producing a partially balanced randomisation. There is a detailed description of withdrawals and drop-outs from the start of the study to completion of the protocol. This included all drop-outs and exclusions that occurred during the pre-randomisation phases. Data on mortality, first hospitalisations and withdrawals for medical reasons were calculated on an intention-to-treat basis; other data were not. There were relatively rigorous inclusion criteria both before trial entry and before entry to the randomised phase.

Results

The results are derived from a single trial (Lowrie, *et al.*, 1983). They are grouped according to the pre-stated outcome measures of this review:

- (i) mortality
- (ii) intra- and interdialytic morbidity
- (iii) measures of dialysis adequacy
- (iv) patient quality of life and patient acceptability.

Data are presented as a comparison of short with standard duration dialysis, subgrouped according to the prescribed dialysis of the allocated groups, standard or low dialysis urea clearance. Dichotomous data are presented as ORs and continuous data as WMDs (see *Table 25*, A and B).

Mortality

One patient from the experimental (short duration dialysis) and two patients from the control group (standard duration) died during the study (OR, 0.53; 95% CI, 0.05, 5.15). Over the study period and follow-up, seven patients in the experimental group and nine in the control group died (OR, 0.79; 95% CI, 0.28, 2.21). Although there was no significant difference in mortality between the two treatment durations, a clinically important difference cannot be ruled out.

Intradialytic morbidity

No data relevant to intradialytic morbidity could be used quantitatively in this review. The single study noted “statistically significant deviations only sporadically during the experimental phase” relative to a symptom questionnaire which attempted to assess the severity of adverse symptoms “commonly associated with dialysis”.

TABLE 24 Characteristics of included studies: short versus standard duration treatments in haemodialysis of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
Lowrie, et al., 1983	Partially-balanced parallel (randomised phase) RCT with adequate concealment of allocation. Open study, although "clinical investigators were blinded to group outcomes throughout the study"; detailed description of withdrawals and drop-outs; some data (mortality and withdrawals for medical reasons) analysed on an intention-to-treat basis.	165 patients with ESRD; M:F, 59.6:40.4; mean age (SD), 49.0 (12.7) years; duration on dialysis (mean, SD), 4.2 (2.3) years; residual renal function: creatinine clearance < 3 ml/min; inclusion criteria – age 18–70 years, RRT > 4 months, creatinine clearance < 3 ml/min on centre dialysis; no more than one missed dialysis treatment per month over previous 3 months, average intradialytic weight gain < 3.5 kg over previous 3 months, average predialysis serum phosphate level < 8.0 mg/dl; exclusion criteria – diabetes mellitus, 'unstable' cerebrovascular or coronary vascular disease, severe or 'unstable' hypertension, significant hepatic or pulmonary dysfunction, 'collagen vascular disease'; in addition to these criteria, to transfer from the control phase to the experimental, randomised phase, the following criteria had to be met during the control phase – 7/10 most recent midweek BUN concentrations within 10 mg/dl of target, no more than two treatments missed in 4 weeks, average intradialytic weight gain < 3.5 kg, average PCR 0.8–1.4 g/kg/day; co-morbidity – no significant difference between groups in terms of age, history of heart disease, hypertension, peripheral vascular disease, pulmonary or gastro-intestinal disease or hospitalisation pre-randomisation.	Patients randomly allocated to four groups: Group I – standard dialysis time (4.5–5.0 hours), low BUN with time-averaged concentration of urea, 50 mg/dl; Group II – standard dialysis time (4.5–5.0 hours), high BUN with time-averaged concentration of urea, 100 mg/dl; Group III – short dialysis time (2.5–3.5 hours), low BUN with time-averaged concentration of urea, 50 mg/dl; Group IV – short dialysis time (2.5–3.5 hours), high BUN with time-averaged concentration of urea, 100 mg/dl. Duration of study, approx. 2.5 years, data collected for 48 weeks after randomisation; dialysis frequency, three times weekly (2.96, SD, 0.18); dialyser type – selected before randomisation – regenerated cellulose membrane (C-DAK, Cordis Dow), surface areas, 1.3 m ² , 1.8 m ² , or 2.5 m ² , or cuprophane membrane (CF, Travenol), surface areas, 1.2 m ² , 1.5 m ² , or 2.3 m ² ; dialysate sodium, 132–140 mmol/l; buffer, all used acetate dialysis (33–40 mmol/l); dialysate flow rate varied for each patient to achieve specified time-averaged urea concentration; blood flow rate varied for each patient (as above); dialyser reuse not mentioned.	Mortality; intradialytic morbidity; general morbidity – withdrawals for medical reasons (excluding renal transplant), cardiovascular morbidity, hospitalisation rate, blood pressure control, symptom questionnaire, EEG and choice reaction time, effect on haematopoietic system; measures of dialysis adequacy – time-averaged urea concentration, midweek pre-dialysis BUN, pre-dialysis phosphate, serum electrolytes, arterial blood gases and pH. Quality of life, general well-being and psychosocial measures – MMPI, SSIAM, SAS-SR, WAIS, LES, I-E, MAACL, symptom questionnaire. Nutritional status, PCR.	Study divided into several phases; final phase (experimental) was only phase with randomly allocated treatments; initiation phase – 1 month, 262 patients; control (plus induction) phase – 12–20 weeks, 224 patients; experimental phase – 165 patients; withdrawals, drop-outs and failure to reach inclusion criteria from initiation of study described in detail. BUN 50 mg/dl ≈ BUN 20 mmol/l; BUN 100 mg/dl ≈ BUN 40 mmol/l.

* MMPI, Minnesota Multiphasic Inventory; SSIAM, Structured and Scaled Interview to Assess Maladjustment; SAS-SR, Social Adjustment Scale Self Report; WAIS, Wechsler Adult Intelligence, vocabulary subscale; LES, Life Events Scale; I-E, Locus of Control Scale; MAACL, Multiple Affect Adjective Check List.

Interdialytic morbidity

The number of patients hospitalised was significantly greater in the short duration dialysis group (33/78 versus 15/73; OR, 2.85; 95% CI, 1.39, 5.85). More patients were withdrawn from the study for medical reasons from the short duration group;

however, this did not reach statistical significance (21/81 versus 14/84; OR, 1.92; 95% CI, 0.85, 4.35).

There was a modest, although significant difference in dialysis treatment duration in predialysis blood pressure control, favouring better control in the

TABLE 25A Short versus standard duration dialysis: overall summary

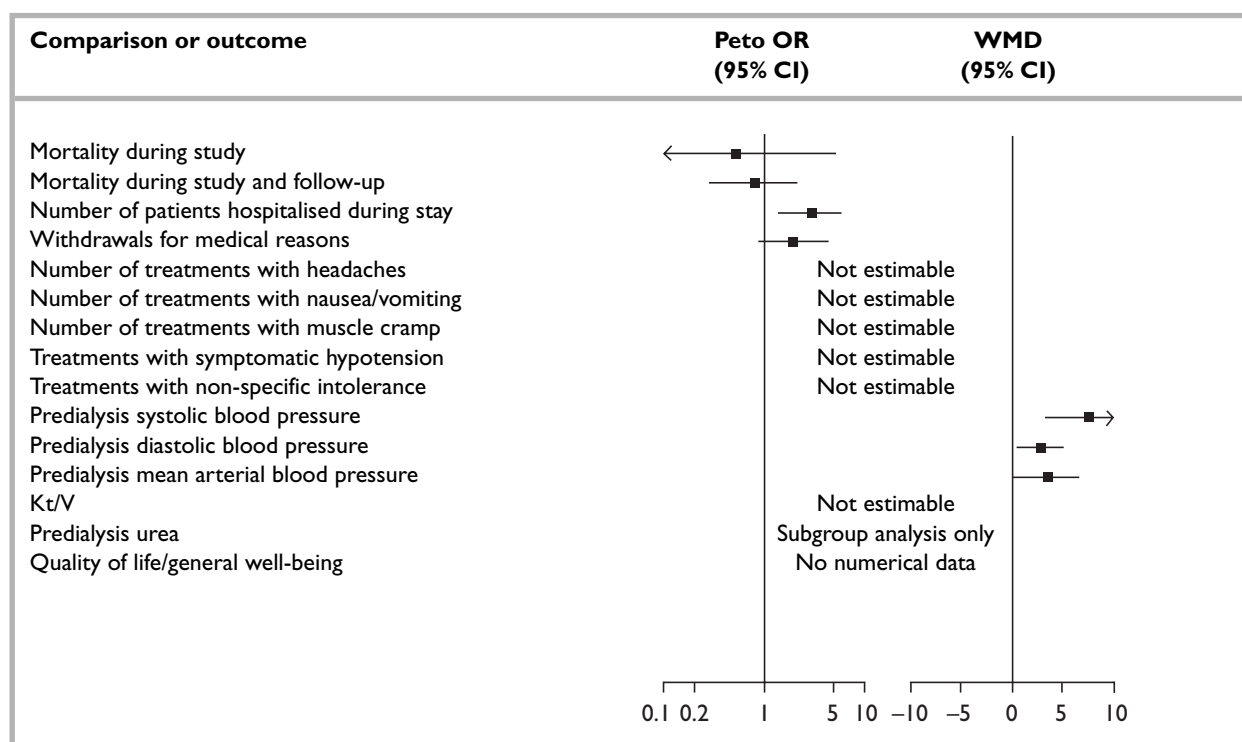
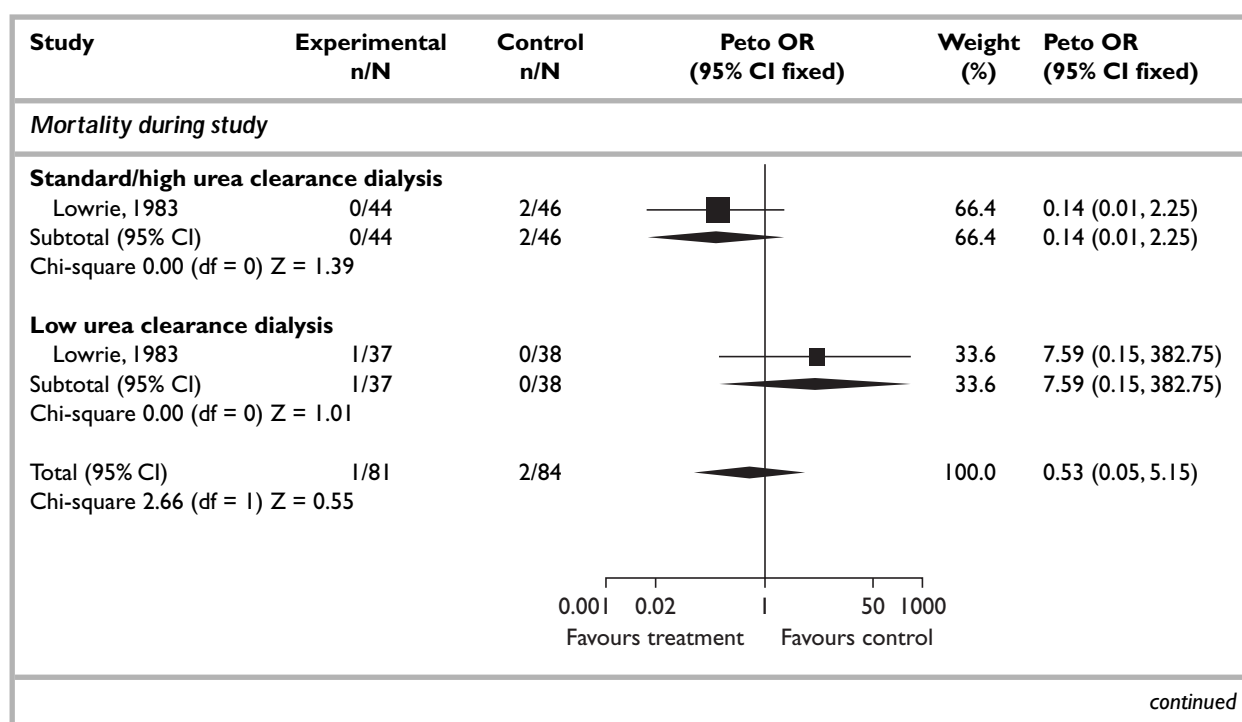


TABLE 25B Short versus standard duration dialysis: detailed meta-analysis



continued

TABLE 25B contd Short versus standard duration dialysis: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Mortality during study and follow-up					
Standard/high urea clearance dialysis					
Lowrie, 1983	2/44	4/46		39.2	0.52 (0.10, 2.69)
Subtotal (95% CI)	2/44	4/46		39.2	0.52 (0.10, 2.69)
Chi-square 0.00 (df = 0) Z = 0.78					
Low urea clearance dialysis					
Lowrie, 1983	5/37	5/38		60.8	1.03 (0.27, 3.87)
Subtotal (95% CI)	5/37	5/38		60.8	1.03 (0.27, 3.87)
Chi-square 0.00 (df = 0) Z = 0.04					
Total (95% CI)	7/81	9/84		100.0	0.79 (0.28, 2.21)
Chi-square 0.41 (df = 1) Z = 0.46					
Number of patients hospitalised during study					
Standard/high urea clearance dialysis					
Lowrie, 1983	11/41	4/41		41.7	3.09 (1.02, 9.40)
Subtotal (95% CI)	11/41	4/41		41.7	3.09 (1.02, 9.40)
Chi-square 0.00 (df = 0) Z = 1.99					
Low urea clearance dialysis					
Lowrie, 1983	22/37	11/32		58.3	2.69 (1.05, 6.90)
Subtotal (95% CI)	22/37	11/32		58.3	2.69 (1.05, 6.90)
Chi-square 0.00 (df = 0) Z = 2.07					
Total (95% CI)	33/78	15/73		100.0	2.85 (1.39, 5.85)
Chi-square 0.03 (df = 1) Z = 2.86					
Withdrawals for medical reasons					
Standard/high urea clearance dialysis					
Lowrie, 1983	3/44	2/46		20.7	1.59 (0.26, 9.58)
Subtotal (95% CI)	3/44	2/46		20.7	1.59 (0.26, 9.58)
Chi-square 0.00 (df = 0) Z = 0.51					
Low urea clearance dialysis					
Lowrie, 1983	18/37	12/38		79.3	2.02 (0.81, 5.05)
Subtotal (95% CI)	18/37	12/38		79.3	2.02 (0.81, 5.05)
Chi-square 0.00 (df = 0) Z = 1.50					
Total (95% CI)	21/81	14/84		100.0	1.92 (0.85, 4.35)
Chi-square 0.05 (df = 1) Z = 1.57					

continued

TABLE 25B contd Short versus standard duration dialysis: detailed meta-analysis

Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Predialysis systolic blood pressure							
Standard/high urea clearance dialysis							
Lowrie, 1983	42	151.00 (13.00)	41	142.00 (12.80)		61.9	9.000 (3.449, 14.551)
Subtotal (95% CI)	42		41			61.9	9.000 (3.449, 14.551)
Chi-square 0.00 (df = 0) Z = 3.18							
Low urea clearance dialysis							
Lowrie, 1983	23	150.00 (14.40)	27	145.00 (10.40)		38.1	5.000 (-2.073, 12.073)
Subtotal (95% CI)	23		27			38.1	5.000 (-2.073, 12.073)
Chi-square 0.00 (df = 0) Z = 1.39							
Total (95% CI)	65		68			100.0	7.475 (3.109, 11.842)
Chi-square 0.76 (df = 1) Z = 3.36							
-100 -50 0 50 100 Favours treatment Favours control							
Predialysis diastolic blood pressure							
Standard/high urea clearance dialysis							
Lowrie, 1983	42	83.00 (6.50)	41	79.00 (6.40)		71.4	4.000 (1.225, 6.775)
Subtotal (95% CI)	42		41			71.4	4.000 (1.225, 6.775)
Chi-square 0.00 (df = 0) Z = 2.82							
Low urea clearance dialysis							
Lowrie, 1983	23	84.00 (9.60)	27	84.00 (5.20)		28.6	0.000 (-4.386, 4.386)
Subtotal (95% CI)	23		27			28.6	0.000 (-4.386, 4.386)
Chi-square 0.00 (df = 0) Z = 0.00							
Total (95% CI)	65		68			100.0	2.856 (0.511, 5.202)
Chi-square 2.28 (df = 1) Z = 2.39							
-10 -5 0 5 10 Favours treatment Favours control							
Predialysis mean arterial blood pressure							
Standard/high urea clearance dialysis							
Lowrie, 1983	42	106.00 (6.50)	41	101.00 (12.80)		61.6	5.000 (0.616, 9.384)
Subtotal (95% CI)	42		41			61.6	5.000 (0.616, 9.384)
Chi-square 0.00 (df = 0) Z = 2.24							
Low urea clearance dialysis							
Lowrie, 1983	23	106.00 (9.60)	27	105.00 (10.40)		38.4	1.000 (-4.548, 6.548)
Subtotal (95% CI)	23		27			38.4	1.000 (-4.548, 6.548)
Chi-square 0.00 (df = 0) Z = 0.35							
Total (95% CI)	65		68			100.0	3.463 (0.023, 6.902)
Chi-square 1.23 (df = 1) Z = 1.97							
-10 -5 0 5 10 Favours treatment Favours control							

standard duration group: systolic blood pressure – mean difference 7.5 mmHg (95% CI, 3.1, 11.8); diastolic blood pressure – mean difference 2.9 mmHg (95% CI, 0.5, 5.2); mean arterial blood pressure – mean difference 3.5 mmHg (95% CI, 0.0, 6.9).

Quality of life and general well-being

There were no data on quality of life or general well-being which could be used quantitatively. The authors of the included study concluded that “no important changes in psychosocial measures can be attributed to the different treatment prescriptions”.

Measures of dialysis adequacy

Midweek predialysis blood urea concentration and time-averaged concentration of urea were used in the study as measures of dialysis adequacy. However, because dialysis treatments were manipulated to achieve a certain dialysis adequacy for each group, these measures were not used as outcome data in this review.

Discussion

The results of this review show that significantly more patients receiving short-duration dialysis were hospitalised. This group also had more withdrawals for medical reasons, although this did not reach statistical significance, and there was also a modest deterioration in blood pressure control. There was no clear difference between the groups in any of the other outcome measures considered. Dialysis adequacy could not be used as an outcome measure because of the structure of the included study. However, a significantly greater number of withdrawals for medical reasons were reported from the low urea clearance groups and, as a result, the short-duration dialysis, low urea clearance group was discontinued early.

Despite the extensive search strategy, only one study was identified in which the inclusion criteria of this review were satisfied (Lowrie, *et al.*, 1983). Although the study was multicentre and relatively large, it comprised a highly selected population with relatively strict inclusion criteria to enter the initial phase. Further criteria needed to be met for a patient to pass forward to the randomised phase of the study. The data may, therefore, be relevant only to this highly selected group who were maintained on dialysis in a particular healthcare system at a particular time (mid-1970s). The composition of the population on dialysis, the dialysis technology and the treatment options for patients with ESRD have all changed since then. For example, older

patients with greater co-morbidity are now accepted on dialysis programmes (Port, 1994), bicarbonate has become the standard dialysate buffer (Vallerrabano, *et al.*, 1996), and the treatment of anaemia has been revolutionised by the introduction of EPO (Winearls, *et al.*, 1986; Eschbach, *et al.*, 1987). The generalisability of the results from this study to patients presently on dialysis and being managed by the presently accepted optimal treatment of ESRD may be questionable.

The obvious significant methodological and organisational difficulties encountered and overcome during the included study may, in part, explain the lack of more recent RCTs in this area. Dialysis clinical research has its own specific problems. The relatively low prevalence of ESRD means that most reasonably sized trials need to be multicentred. The high withdrawal and drop-out rate demonstrated by this study is likely to be an inevitable consequence of the morbidity of this population and the potential for withdrawal because of renal transplantation. This may have encouraged other researchers to attempt to predict long-term clinical outcomes from data on surrogate outcomes derived from short-term studies. However, the ability of these secondary outcome measures to predict long-term clinical outcomes remains open to question.

Dialysis adequacy and duration are interlinked. Changes in dialysis adequacy can be achieved by altering other dialysis technique parameters, such as blood flow rate, dialysis membrane size and membrane flux. Reduced dialysis adequacy appears to have a definite adverse effect on outcome; however, whether reduced dialysis time alone has an adverse effect is less clear.

A large, multicentre, 2 × 2 factorial RCT, which compares the effect of dialysis dose and membrane flux on survival of patients with ESRD, is currently being conducted in the USA and is due to be completed in 2001. The principal investigator of the study is Dr John Kusek of the National Institutes of Health. The aim is to recruit 1700 patients to the study; to date, more than 1000 patients have been recruited. Although the results of the study may answer the questions of how much dialysis is needed and how that amount of dialysis may be delivered, the specific aim is to study the effect of different levels of dialysis adequacy as measured by Kt/V (equilibrated Kt/V of 1.05 versus 1.45) rather than dialysis duration *per se*. Preliminary baseline data has already been reported (Eknoyan, 1997; Levey, 1997; Maroni, 1997; Meyer, 1997a; b). It may be that changes in

the management of patients with ESRD, such as EPO, bicarbonate dialysis and high-flux membranes may have altered the influence of dialysis duration on clinical outcome.

Dialysis duration must seem a very fundamental concept to patients, their relatives and purchasers of renal services. If dialysis time can be shortened safely then this should be done. However, good evidence of such safety does not yet exist and, until it becomes available, the standard duration regimen should be continued. If short-duration dialysis is used, patients should be made aware that its effects on morbidity and mortality remain unknown.

Given the interest in shortening the length of haemodialysis sessions, it is disappointing that only one RCT was identified that addressed this question. An economic evaluation was attempted but there was insufficient information to enable judgements to be made about the relative efficiency of short-compared to standard-duration haemodialysis. In particular, the RCT was not performed on an intention-to-treat basis, which meant that important information on patient outcomes was not collected when patients were withdrawn from the trial.

Conclusions and implications

Policy implications

1. Current evidence is not reassuring that short-duration dialysis is as effective as standard-duration dialysis. There is no evidence that reduced dialysis duration improves patient outcome in terms of mortality and morbidity, and it may in fact increase morbidity as reflected by increased hospitalisation and poorer blood pressure control. Standard-duration dialysis should remain the recommended treatment.
2. If reduced dialysis duration regimens are implemented on the basis of patient preference or cost, the fact that its safety is not proven should be explicitly acknowledged.

Future research needs

1. A large, multicentre, pragmatic RCT(s) that compares haemodialysis treatment duration policies is required. Such a trial should have minimum exclusion criteria, a long follow-up period and minimum data collection, concentrating primarily on patient morbidity and mortality. Follow-up should include patients who withdraw (for example, for renal transplantation) and all patients should be followed

for a period after trial completion to assess the residual effect on mortality and morbidity. Key primary outcomes such as mortality should be analysed on an intention-to-treat basis. Avoidance of collection of secondary outcome data should reduce the complexity of such a trial. Dialysis therapy and the overall treatment of ESRD within such a trial should be to the highest standard, as recommended by the best available evidence.

2. If such a trial showed no advantage with standard-duration dialysis, short-duration dialysis should become the recommended treatment option.
3. The HEMO RCT, comparing high- and low-flux membranes and the ability to achieve a given Kt/V , is under way at present. It may address many of the above questions. This should be taken into account when the research agenda is decided.

References

Studies included in the review

Note: these references all refer to one study; hence, the citation (Lowrie, *et al.*, 1983) refers to them all.

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Lowrie E, 1983. History and organization of the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S1–7.

Wineman R, 1983. Rationale of the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S8–10.

Sargent J, 1983. Control of dialysis by a single-pool urea model: the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S19–25.

Olivier D, Nash B, 1983. Data management, data analysis, and statistical methods in the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S26–30.

Frankel R, Engel R, Olivier D, Halpern E, 1983. Laboratory quality control in the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S31–6.

Parker T, Reed R, Lowrie E, 1983. Description of the participating centers and the patient population in the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S37–41.

Parker T, Laird N, Lowrie D, 1983. Comparison of the study groups in the National Cooperative Dialysis Study and a description of morbidity, mortality, and patient withdrawal. *Kidney Int*;23 suppl 13:S42–9.

Maher B, Lamping D, Dickinson C, Murawski B, Olivier D, Santiago G, 1983. Psychosocial aspects of chronic hemodialysis: the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S50–7.

Teschner P, Bourne J, Reed R, Ward J, 1983. Electro-physiological and neurobehavioural responses to therapy: the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S58–65.

Teehan B, Laird N, Harter H, 1983. Influences of dialysis prescription on electrolyte and acid–base metabolism: the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S66–72.

Harter H, Laird N, Teehan B, 1983. Effects of dialysis prescription on bone and mineral metabolism: the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S73–9.

Schoenfeld P, Henry R, Laird N, Roxe D, 1983. Assessment of nutritional status of the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S80–8.

Rao T, Roxe D, Laird N, Santiago G, 1983. Hemodynamic and cardiac correlates of different hemodialysis regimes: the National Cooperative Dialysis Study. *Kidney Int*;23 suppl 13:S89–94.

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Studies excluded from the review (with reason for exclusion)

Alfurayh O, Galal O, Sobh M, Fawzy M, Taher S, Qunibi W, *et al.*, 1993. The effect of extracorporeal high blood flow rate on left ventricular function during hemodialysis – an echocardiographic study. *Clin Cardiol*;16:791–5.

(Treatments randomly allocated according to blood flow rates. Varying treatment times were an outcome of the various blood flow rates (Kt/V was to be maintained) rather than the primary reason for treatment group allocation. None of the published outcomes were included in this review's criteria for types of outcome.)

Lindsay R, Spanner E, Heidenheim A, Burton H, Lindsay S, LeFebvre J, 1991. A multicenter study of short hour dialysis using AN69S. Preliminary results. *ASAIO Trans*;37:M465–7.

(Not all patients randomly assigned. Those randomised were “supplemented by matched cohort samples” and it was not possible from the published data to distinguish randomised patients.)

Lindsay R, Spanner E, Heidenheim R, LeFebvre J, Hodsmann A, Baird J, *et al.*, 1992. Which comes first, Kt/V or PCR – chicken or egg? *Kidney Int*;42 suppl 38:S32–6. (Patients were randomly allocated to either an unchanged Kt/V group or to an increased Kt/V group. Variation in duration of dialysis would have been only one component of the varied Kt/V and was not described separately.)

Ward R, Farrell P, Tiller D, Horvath J, Freeman J, 1976. A clinical evaluation of large-area short-time haemodialysis. *Aust N Z J Med*;6:288–91.

(Crossover study but only A–B–A. Allocation to first treatment was not randomised.)

On-going studies

The HEMO study. <http://www.nrtc.uab.edu/hemo.html>

General references

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Port F, 1994. Morbidity and mortality in dialysis patients. *Kidney Int*;46:1728–37.

Vallerrabano F, Berthoux FC, Jones E, Mehls O, 1996. Report on management of renal failure in Europe, XXV, 1994. End stage renal disease and dialysis report. *Nephrol Dial Trans*; **11** suppl 1:2–21.

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Appendix 7

Systematic review 4: Comparison of CAPD delivery systems – Y-set/modified Y-set versus standard spike as treatment for patients with ESRD

Background

CAPD is an alternative to haemodialysis for patients with ESRD. It may be used as the first choice therapy, and in a number of countries more patients are treated by CAPD than by haemodialysis. There is significant variation in catheter and transfer set types, insertion techniques, and peri- and postoperative management of patients. Rates of complications (exit-site leak, exit-site infection, subcutaneous tunnel infection, catheter cuff erosion or prolapse, catheter malfunction, pericatheter hernia/pseudohernia, posterior peritoneal perforation, postoperative bleeding, hollow viscus perforation) and catheter survival also vary between centres,

There are two main types of catheter connecting systems.

1. The standard or straight connecting system in which the catheter is connected with a straight piece of tubing which is, in turn, connected to the dialysate bag. At each exchange the bag is drained and a new connection is made. The empty bag is rolled up and remains attached until the next exchange when the process is repeated.
2. The Y-set in which, between exchanges, the patient is disconnected from dialysate bags and, when a new exchange is due, a Y-connection with one limb connected to an empty bag and one to a bag containing fresh dialysate is used. The peritoneal dialysate is first drained into the empty bag. Before introducing the new fluid, the Y-connector is flushed with fresh dialysate into the drained bag. This allows any bacteria to be flushed into the spent fluid. The fresh fluid is then introduced into the peritoneal cavity and the connector is removed from the catheter.

At present, about 40% of CAPD patients in the UK use the standard system (data from Renal Registry, presented at Renal Association meeting, 1997).

The aim of this review is to describe the best practice for CAPD connecting systems, insofar as present evidence allows, and to indicate areas for future research.

Objective

The objective of this review is to compare Y-transfer set systems or their modification with standard non-Y systems in CAPD.

Materials and methods

Criteria for considering studies for this review

Types of studies All RCTs or quasi-RCTs addressing the objective.

Types of participants All CAPD patients newly commenced on this modality of RRT were included in the studies considered.

Types of intervention The use of Y-set (or modifications thereof) using flush-before-fill and either hypochlorite or povidone iodine disinfectant compared with standard non-Y-set connection systems for the delivery of CAPD to patients starting on this modality of RRT.

Types of outcome measures The following outcome measures were considered:

- (i) peritonitis
- (ii) exit-site infections.

Search strategy for identification of studies

The search strategy used was one developed for the identification of all possible RCTs or quasi-RCTs relating to the management of ESRD, and is described in detail in chapter 2 and appendices 2 and 3.

Methods of the review

All included studies were evaluated using a study evaluation form and those which met the eligibility criteria (included references) were then considered in detail. Data were extracted using a data abstraction form designed for this review (see appendix 10). Review Manager v. 3.0 was used for the analysis. A full description of the methods used is given in chapter 2.

Description of studies

A total of six studies met the inclusion criteria for this review. Two reports were of the same study (Maiorca, *et al.*, 1983a; b); hence the data were considered only once. All six studies were either RCTs or quasi-RCTs in which Y-transfer sets were compared with standard non-Y-set systems. A summary of the included studies is presented in *Table 26*.

Methodological quality of included studies

All studies claimed to have random allocation and owing to the nature of the intervention, blinding was not possible. The methods of randomisation were adequately described in three studies (Cheng, *et al.*, 1994 (random number tables); Maiorca, *et al.*, 1983a; b (envelopes); Canadian CAPD Clinical Trials Group, 1989 (variable blocking factor)). All studies provided numbers and reasons for patient withdrawals and drop-outs.

Results

Peritonitis rates

The number of patients who experienced at least one episode of peritonitis in all the studies combined was significantly lower in patients using the Y-set delivery systems (57/194; OR, 0.30; 95% CI, 0.23, 0.53) compared with those assigned to the non-Y-set systems (107/201; OR, 0.87; 95% CI, 0.51, 1.48). Only one study (Cheng, *et al.*, 1994) did not show this effect although all the studies demonstrated a significant increase in the number of months per episode of peritonitis using Kaplan-Meier survival analysis. None of the studies provided standard deviations for this statistic and, hence, no WMD could be obtained. All studies showed that time to first peritonitis was longer with use of Y-set/modified Y-set systems.

Exit-site infections

There was no evidence of significant reductions in the number of patients who suffered exit-site or tunnel infections with the Y-set (39/162 in the treatment group and 44/171 in the control group;

OR, 0.87; 95% CI, 0.51, 1.48). The meta-analysis of the results is presented in *Table 27* (A and B).

Discussion

This review shows that use of the Y-set delivery systems in CAPD significantly reduces the incidence of CAPD-related peritonitis. The flush-before-fill technique, combined with the use of a disinfectant (hypochlorite or povidone iodine) is considered to lead to this improvement. CAPD-related peritonitis is the Achilles heel of this modality of RRT and repeated infections of the peritoneum and/or intractable episodes of peritonitis are the major causes of morbidity, technique failure and, often, mortality in such patients. This review clearly demonstrates the benefit of Y-set delivery systems over non-Y-set systems in preventing this major complication of CAPD. The incidence of exit-site infections was not affected by the delivery system. This suggests that the reduction in peritonitis seen with the Y-set systems is not consequent upon a reduction of exit-site infections but is probably caused by the 'washing' of organisms in the tubing by the flush-before-fill technique.

Economic evaluation

The principles of economic evaluation are described in detail in chapter 3 (page 9) including, in an economic framework, the manner in which costs and outcome are related (see, in particular, *Table 2* and *Figure 3*).

Aims

CAPD is an alternative to haemodialysis in which various alternative techniques are used. One way in which techniques can vary is in the transfer set types that are used. The aim of this economic evaluation is to assess the relative efficiency, using the framework of economic evaluation outlined in chapter 3, of Y-set systems or their modifications compared with standard non-Y-set systems for delivering CAPD. More specifically, the aims of this economic evaluation are:

- (i) to investigate the relative resources used and the cost of Y-set systems or their modifications compared with standard non-Y-set systems for delivering CAPD, using data extracted from the identified RCTs and non-randomised studies in which the two delivery systems are compared
- (ii) to combine data on cost with those on benefits to patients, from the systematic review of effectiveness described above,

TABLE 26 Characteristics of included studies: comparison of CAPD delivery systems – Y-set/modified Y-set versus standard spike

Study	Method	Participants	Interventions	Outcomes	Notes
Canadian CAPD Clinical Trials Group, 1989	RCT; numbers and reasons for withdrawals stated; no mention of blinding; analysis on intention-to-treat basis.	124 new CAPD patients – from 159 consenting patients eligible for inclusion, 61 in study group, 63 in control group; M:F, not stated; exclusion criteria: age < 18 years, likely to die within 6 months, previous complications on CAPD.	Y-connector (Amuchina) vs. standard spike (Baxter II and III).	Peritonitis; exit-site infections; technique survival (Kaplan-Meier).	Hypochlorite disinfectant in Y-set.
Cheng, et al., 1994	RCT; numbers and reasons for withdrawal stated; not clear if analysis on intention-to-treat basis; no mention of blinding.	All 100 patients starting CAPD over 2 years at a tertiary referral and satellite center; 38 in treatment group, 31 in control group; M:F, 20:18 in treatment group, 17:14 in control group; diabetes, one in treatment group, three in control group; exclusion criteria: age < 10 or > 70 years, renal transplant within 6 months of treatment, inability to afford Y-set.	Y-set (O-set) vs. conventional spike vs. ultraviolet irradiation (excluded from this review).	Peritonitis; exit-site infections; costs.	Hypochlorite disinfectant used.
Dryden, et al., 1992	Prospective RCT; numbers and reasons for withdrawals stated; analyses on intention-to-treat basis; no mention of patient or investigator blinding.	80 patients, 40 in treatment group, 40 in control group; 57% M in treatment group, 65% M in control group; diabetes, five in treatment group, seven in control group; study period, 3–36 months (mean, 14.1); age range, 20–67 years (mean 49).	Y-set (Freeline Solo) vs. standard spike (Baxter II).	Peritonitis.	Hypochlorite not used in this system; povidone iodine cap protectors used.
Maiorca, et al., 1983a; b	RCT; numbers and reasons for withdrawals stated; no mention of patient or investigator blinding.	62 new CAPD patients, 32 in treatment group, 30 in control group; mean age (SD), 55.1 years (14.3) in treatment group, 55.5 years (17.5) in control group; M:F, 15:17 in treatment group, 11:19 in control group; inclusion and exclusion criteria not mentioned; co-morbidity and renal diagnoses not mentioned.	Y-connector with disinfectant (Travenol, Lessines) vs. standard spike (Travenol).	Peritonitis episodes.	Hypochlorite used; Kaplan-Meier analysis for time to peritonitis showed improvement with Y-set. Second reference is to exactly the same study.
Owen, et al., 1992	Prospective RCT; states random allocation but no description; numbers and reasons for withdrawals stated.	60 consecutive CAPD patients from 83 commencing, 30 in treatment group, 30 in control group, followed for minimum of 12 months; median age, treatment group 54 years (range, 11–79 years), control group 56 years (range, 16–75 years); M:F, 16:14 in treatment group, 15:15 in control group; inclusion criteria, starting CAPD after May 1987; exclusion criteria, blind or severely physically disabled.	Flush-disconnect (O-system, Baxter) vs. standard spike (Baxter II).	Peritonitis; exit-site infection; costing.	Povidone iodine caps used; Kaplan-Meier analysis also performed.

TABLE 27A Y-set/modified Y-set versus standard spike delivery system: overall summary

Comparison or outcome	Peto OR (95% CI)	WMD (95% CI)
Peritonitis episodes (number of patients)	Not estimable	
Peritonitis episodes (months per episode)	Not estimable	
Exit-site infections (patient numbers)	Not estimable	
Exit-site infections (months per episode)	Not estimable	

TABLE 27B Y-set/modified Y-set versus standard spike delivery system: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Peritonitis episodes (number of patients)					
Canadian, 1989	15/61	30/63		31.7	0.37 (0.18, 0.77)
Cheng, 1994	9/31	12/38		16.1	0.89 (0.32, 2.47)
Dryden, 1992	9/40	21/40		20.8	0.28 (0.11, 0.69)
Maiorca, 1983a; b	10/32	17/30		17.0	0.36 (0.13, 0.98)
Owen, 1992	14/30	27/30		14.5	0.14 (0.05, 0.41)
Total (95% CI)	57/194	107/201		100.0	0.35 (0.23, 0.53)
Chi-square 6.22 (df = 4) Z = 5.03					
Favours treatment Favours control					
Exit-site infections (number of patients)					
Canadian, 1989	21/61	23/63		52.2	0.91 (0.44, 1.90)
Cheng, 1994	1/31	4/38		8.5	0.34 (0.06, 2.11)
Dryden, 1992	3/40	4/40		11.8	0.73 (0.16, 3.43)
Owen, 1992	14/30	13/30		27.5	1.14 (0.42, 3.13)
Total (95% CI)	39/162	44/171		100.0	0.87 (0.51, 1.48)
Chi-square 1.35 (df = 3) Z = 0.51					
Favours treatment Favours control					

to assess the relative efficiency of Y-set systems or their modifications compared to standard non-Y-set systems for delivering CAPD.

Methods

Data collection and extraction

The methods used are described in detail in chapter 3 of the main report.

Benefits to patients

The systematic review of RCTs or quasi-RCTs described above had as its main objective the synthesis of the effectiveness data from the RCTs. Information was extracted from the RCTs on the following:

- (i) the frequency of peritoneal dialysis-associated peritonitis
- (ii) the frequency of exit-site and tunnel infections.

Identification of resource use and costs

The overall costs of CAPD using the two forms of delivery system were not elicited. Only in those areas where there was likely to be some difference in resource use were costs identified. When patients were dialysed using either of the two delivery systems, the identification of the relative resources used involved the following.

1. Defining the process of care so that all aspects of care in which resources were consumed could be identified and compared. The process of care comprises dialysis access and training, dialysis exchanges, dialysis maintenance including routine outpatient visits, treatment of complications and changes in modality of treatment.
2. All relevant information on resource use was abstracted from the RCTs on what resources were used when utilisation differed between the two modes of delivery. The process was repeated for those studies that were not randomised and the information combined with estimates of the unit cost of the resources to determine the cost differential between Y-set systems and standard non-Y-set systems for delivering CAPD using the methodology described below. This differential could then be compared with data on benefits to patients obtained from the systematic review of effectiveness.

Model of costs

Five main areas of resource use can be costed. These reflect the sequence of the treatment process outlined above.

1. **Catheter insertion** Peritoneal dialysis requires a catheter to be inserted to provide access to the peritoneum. Haemodialysis may be required until peritoneal dialysis can be performed. For peritoneal dialysis using either delivery system the process of inserting the catheter would be the same; hence, the resources which would be consumed would also be the same.
2. **Training** Once the catheter has been inserted a patient requires to be trained in the use of peritoneal dialysis. This training takes several weeks and can be performed as either an in- or outpatient procedure. While undergoing training, patients may require haemodialysis until they are trained in peritoneal dialysis. For simplicity it has been assumed that the resources required for training are the same although the training may differ for each mode of delivery of CAPD.
3. **The dialysis process** Costs of capital items, any consumables used and any staff inputs for the

process of dialysis were calculated. Patients also required routine outpatient visits which were not costed as they were assumed to be identical for both Y-set and standard non-Y-set systems.

4. **Treatment of complications** The cost of treating complications was also calculated by using the model depicted in *Figure 11*. Data were abstracted from the RCTs on the relative probability of the complications. The review of RCTs and non-randomised studies attempted to identify the precise treatment that was provided for a specific complication. The treatments were then costed according to the staff, consumables, overheads and capital that the treatment consumed. The price of any pharmaceuticals consumed was taken from the BNF (BMA, 1996), and the cost of staff time was estimated by combining information on time with that from the relevant UK NHS salary scales (NHS, 1996a; b).
5. **Changes in modality and death** Costs (and outcomes) would be determined by the probability of technique failure and transplantation over a given period (e.g. a month or year). The probability of technique failure can be divided into the probability of transferring to another mode of treatment, for example, transplantation, or dying, so allowing the inclusion, if necessary, of the cost of managing patients after they had switched modality.

A simplified version of how these costs and probabilities can be modelled is shown in *Figure 11*. For any given period a patient would incur the cost of treatment (the CAPD exchanges) and the cost of a complication (based on the cost of treating that complication once it has occurred and the probability of the complication occurring). At the end of that time, a patient would have the chance of 'dropping-out' of treatment by either dying or receiving a renal transplant or transferring to another mode of dialysis (where appropriate the costs would be estimated). If the patient does not drop out then they return to another period of CAPD (indicated in *Figure 11* by the movement from 'A₁' back to 'A' or 'B₁' back to 'B').

Results

Benefits to patients

The number of patients who experienced one episode of peritonitis was significantly lower in patients using the Y-set delivery system (57/194) compared with the standard non-Y-set system (107/201). There was no significant increase in the number of patients who suffered exit-site or tunnel infections.

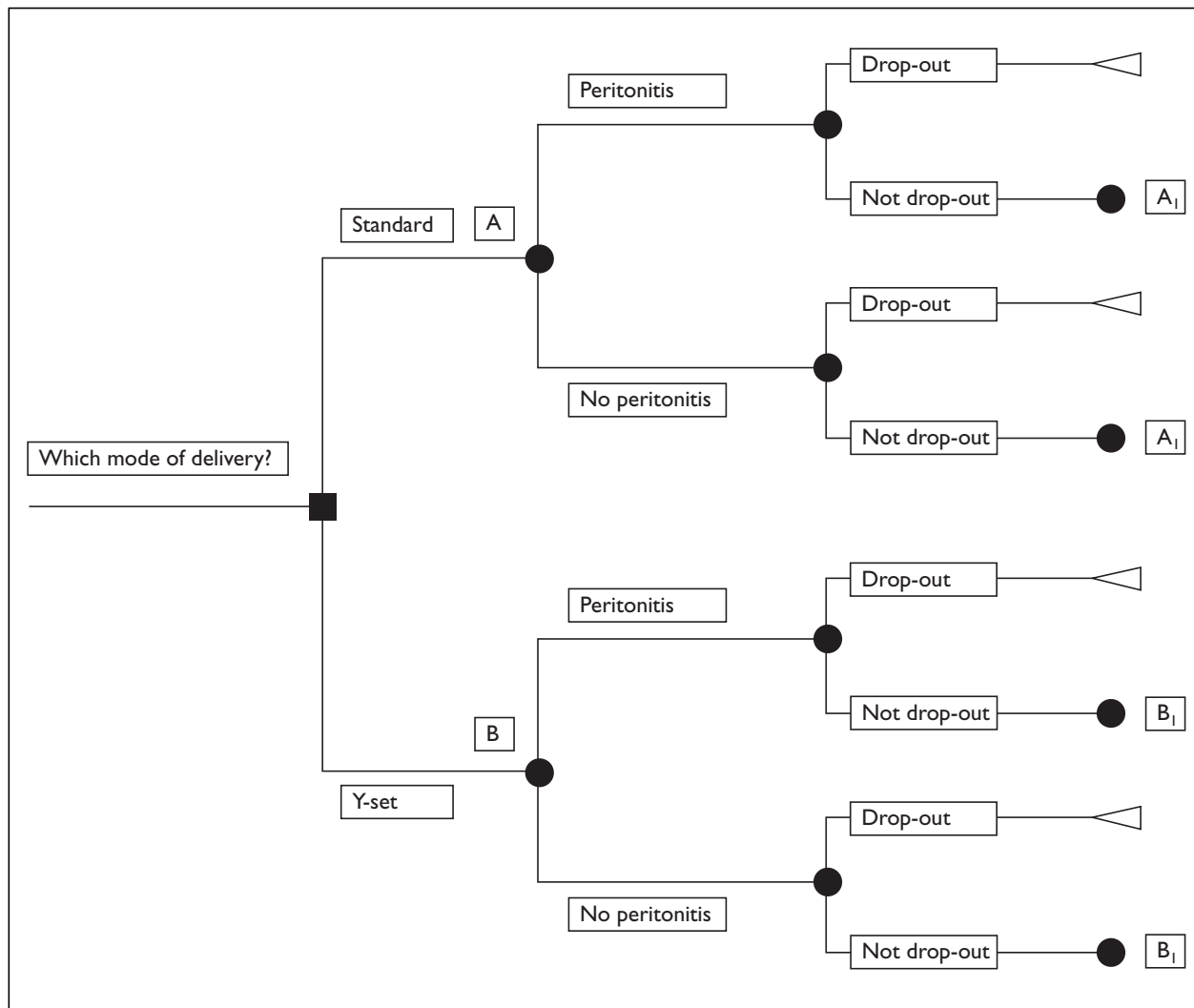


FIGURE 11 Decision model to compare the alternative forms of dialysis (■, decision node; ●, chance node; ◁, terminal node)

Resource use and costs

The principle cost differences between the Y-set and standard non-Y-set systems for delivering CAPD result from differences in the cost of the two processes of dialysis and the cost of treatment of complications.

Resources used before and during the dialysis session

It has been assumed that the resources used and the costs of the initial insertion of the catheter and of training the patient to use their designated mode of peritoneal dialysis are the same for both methods of delivery.

Cost of peritoneal dialysis

The cost per patient per month of Y-set and standard non-Y-set systems for delivering CAPD are shown in *Tables 28* and *29*. It includes the capital costs and the cost of consumables used in the dialysis process. The cost of routine check-ups

have, however, not been included as these have been assumed to be the same for patients treated by either the Y-set or the standard non-Y-set system. All exchanges are assumed to be performed by the patient or the patient's carer. The time that the patient or carer spends in performing exchanges has not been estimated but may differ between the two modalities.

Cost of complications

The evidence presented in the 'benefits to patients' section above suggests that the rate of peritonitis differed between patients dialysed with either Y-set or standard non-Y-set systems. Insufficient data were reported in the systematic review of effectiveness for an economic analysis to be undertaken. The only outcome measure for peritonitis suitable for meta-analysis did not provide any information on the period over which data was collected on peritonitis or the number of peritonitis episodes that occurred within that period. In order to obtain

TABLE 28 The cost per month per patient of CAPD using the Y-set system

Item	Number of items per day	Cost per item (£)		Cost per month (£)	
		Low	High	Low	High
2 litre fluid	4	4.7	5.3	571.83	644.83
Cap	4	0.45	0.45	54.75	54.75
Shield	4	0.45	0.45	54.75	54.75
Total				681	754

TABLE 29 The cost per patient per month of CAPD using the non-Y-set system

Item	Number of items per day	Cost per item (£)	Cost per month (£)
2 litre fluid	4	3.5	425.83
Transfer set (one per year)		9.3	0.77
Total			427

estimates of the probabilities and periods required, the included studies from the systematic review of effectiveness were further analysed.

There was insufficient evidence in the included RCTs to suggest that the probability of death, transfer to haemodialysis, or renal transplant differed between patients starting CAPD using either the Y-set or the standard non-Y-set system. There was also insufficient evidence to suggest that the probability of technique failure is different (analogous to 'drop-out' in *Figure 11*). Of the three studies that reported technique failure, the Canadian CAPD Clinical Trials Group (1989) found no statistically significant differences in technique survival between patients started on CAPD with the Y-set compared with the standard non-Y-set systems. Cheng and colleagues (1994) reported that the technique survival was comparable and Dryden and colleagues (1992) reported technique failure to be greater in patients receiving CAPD with the standard non-Y-set system than with the Y-set system. This result, however, was not statistically tested.

The estimates for the relative probability of developing peritonitis for patients who started on CAPD with Y-set system and the standard non-Y set systems are shown in *Table 30*. As no single estimate could be obtained from meta-

analysis, high, medium and low estimates of cost have been calculated from data in the literature. These estimates are based upon the number of patient-months of care, on average, before one episode of peritonitis occurred.

The cost per episode of peritonitis is shown in *Table 31*.

Using the model depicted in *Figure 11*, the data included in *Tables 28–31* can be used to calculate the relative cost per patient of CAPD using either the Y-set or standard non-Y-set system. A summary of the sensitivity analysis of the incremental cost of patients treated on the Y-set and standard non-Y-set system is shown in *Table 32*. The high and low estimates are based on the assumptions that are most favourable and least favourable to the Y-set system. For example, for the low estimate presented in *Table 32*, the calculation of cost is based upon the low cost of CAPD using the Y-set system (see *Table 28*) minus the cost of the non-Y-set system (see *Table 29*) plus the high cost of peritonitis treatment (*Table 31*) which has been

TABLE 30 The extra probability of an episode of peritonitis per month for patients who started CAPD with the standard non-Y-set system compared with patients who started CAPD with the Y-set system

	Relative probability per month	Data source
Low	0.014	Cheng, et al., 1994
Medium	0.054	Canadian CAPD Clinical Trials Group, 1989; Maiorca, et al., 1983b
High	0.129	Owen, et al., 1992

TABLE 31 Cost per episode of peritonitis

Item of resource use	Cost per episode (£)	
	Low	High
10-day course of antibiotics		
Vancomycin (10 vials 250 mg plus 2 × 500 mg injections)	65	65
Serum concentration (1 per day)	300	300
Syringe	12	12
Hospitalisation (0 for 'Low', 5 days for 'High')	0	996
Total	377	1373

TABLE 32 The incremental cost of CAPD per patient per month of the Y-set and standard non-Y-set systems

Additional cost of Y-set over non-Y-set	Cost per patient per month (£)
Low	77
Medium	254
High	322

multiplied by the high probability of avoiding a peritonitis episode by using the Y-set system (see figures from Owen *et al.*, 1992, in *Table 30*).

Combining costs and benefits

The combination of the information on the relative effectiveness and cost of the Y-set and standard non-Y-set systems for CAPD can provide information on the relative efficiency of the alternatives. The available information on benefits suggests that the Y-set system provides more benefits to patients than the standard non-Y-set system. Crucial information required to estimate the cost was not available in a sufficiently robust form to allow a definitive calculation of cost. Therefore, in terms of the framework described in *Figure 3* (page 10), the results suggest there is insufficient evidence on costs to make a judgement on the relative efficiency of the two delivery systems (area D1 on the matrix linking effectiveness and cost). If the available information is used, then the Y-set systems are both more effective and more costly than the non-Y-set systems (area C1 of the matrix). In this area a judgement is required on whether the extra benefits are worth this additional cost. Additional information can be obtained from the data by using incremental analysis, that is, by identifying the extra resources required to achieve one more of a beneficial effect. This allows a more explicit consideration of the opportunity cost of Y-set systems in preference to the non-Y-set systems. An opportunity cost is defined in terms of the benefits that could have been obtained if the resources were used in their next best alternative use. The consequence of using limited resources in one way is that the opportunities to use them in other desirable ways are forfeited. The cost of that decision is the

benefit that could have been obtained by using the resources in other desirable ways.

Using the data shown in *Tables 30* and *32*, the additional cost of preventing one case of peritonitis when patients are started on CAPD using the Y-set rather than the non-Y-set system can be calculated (*Table 33*). In this table, it is important to note that the higher the probability of avoiding a case of peritonitis then the lower the cost of the more effective Y-set at preventing peritonitis.

The low and high cost-effectiveness ratios shown in *Table 33* are based upon the very best and the very worst assumptions considered when comparing Y-set with non-Y-set systems.

Discussion

It was not possible to definitively estimate the relative costs of the two delivery systems and, hence, it was not possible to estimate relative efficiency. Available data suggested that the Y-set system was more effective but more costly than the non-Y-set system. A judgement is therefore required as to whether the additional costs of starting a patient on CAPD using the Y-set system are worth the additional benefits it provided compared with starting a patient on CAPD using the non-Y-set system.

It has been assumed that technique survival is the same with both delivery systems. The two studies that explicitly report technique survival (Canadian CAPD Clinical Trials Group, 1989; Dryden *et al.*, 1992) reported that survival was greater with the Y-set system but that the difference failed to reach statistical significance and that it was not possible to perform a meta-analysis of this data. If patients using the non-Y-set method have more chance of switching to haemodialysis because of technique failure, then this would tend to improve the relative efficiency of the Y-set system compared to the non-Y-set system.

With respect to this economic evaluation a number of comments can be made. Costs are derived from estimates of resource use and probabilities which are directly taken from studies conducted in different settings. There are questions as to how generalisable

TABLE 33 The additional cost per patient on CAPD with the Y-set system for episodes of peritonitis avoided

Additional cost per patient per month (£)	Reduction in probability of peritonitis with Y-set system	The extra cost (£) per patient per case of peritonitis avoided
Low 77	High 0.129	597
Medium 254	Medium 0.054	4704
High 322	Low 0.014	23,000

such data could be. The quantity of resources consumed in any given setting are influenced by their prices which can, and do, vary between settings.

Further work is required to establish differences in the long-term costs and outcomes of the two methods of CAPD delivery. It may be possible, using sensitivity analysis, to gain robust estimates of long-term costs and outcomes by identifying data from well-designed prospective observational studies.

Conclusions and implications

Policy implications

Peritonitis is one of the main complications of CAPD and is known to lead to morbidity, technique failure and mortality. Based on the results of this review, there is insufficient evidence to support the continued use of non-Y-set connecting systems in CAPD. The economic evaluation of this review reveals that the use of a Y- or modified Y-set connector imposes an incremental cost of £77–322, based on low and high cost estimates. The additional cost of the Y-set system is £327 compared with the standard system (Baxter Ltd, personal communication). In order to prevent one episode of peritonitis, however, wide variations in cost for Y-set or modified Y-set systems were estimated depending on the relative probability of peritonitis per month.

If it is assumed that there is a higher incidence of technique failure with standard set systems, then the use of the Y-set or modified Y-set system is cost efficient.

Future research needs

Peritonitis remains a major problem in CAPD and further research into methods of prevention of this complication is required.

References

Studies included in the review

Canadian CAPD Clinical Trials Group, 1989. Peritonitis in continuous ambulatory peritoneal dialysis (CAPD): multi-center randomised clinical trial comparing the Y connector disinfectant system to standard systems. *Perit Dial Int*;9:159–63.

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British Medical Association and The Pharmaceutical Press, 1996. British National Formulary (September 1996). Bath: Bath Press.

NHS, 1996a. Pay and conditions of service: remuneration of hospital, medical and dental staff and doctors in public health medicine and the community health service. Edinburgh: Scottish Office: National Health Service in Scotland, NHS circular PCS (DD)1996/4.

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Appendix 8

Systematic review 5: Comparison of CCPD with CAPD as treatment for patients with ESRD

Background

CAPD has been used as an alternative to haemodialysis for patients with ESRD since 1976 (Popovich, *et al.*, 1976). CCPD, in which most of the dialysis exchanges are performed during the night with the aid of an automated cyclor machine is a modification of CAPD. In CAPD, at least four 1.5–3.0 litre exchanges are required daily; each exchange must be performed by the patient (or carer). However, in CCPD only one connection/disconnection procedure is required; all the exchanges (variable number and variable volume) are performed automatically by the automate cyclor machine. CCPD was initially introduced as an alternative to CAPD for those patients who experienced difficulty with CAPD or in whom it could be predicted that difficulty with CAPD might be encountered. For example, parents of young children with ESRD could be freed from performing daytime exchanges and older children would no longer have to perform exchanges at school, away from the privacy and controlled environment of their homes. Patients who had difficulty performing CAPD exchanges because of a disability, such as a neurological deficit or reduced vision, could benefit either from the reduced number of procedures or the possibility that a relative or partner could perform the connection/disconnection procedures (Diaz-Buxo, 1985). Patients who have a rapid rate of solute transfer across their peritoneal membranes (high transporters) were also considered to be likely to benefit from CCPD, because of the ability to perform rapid frequent exchanges with short dwell-times.

More recently, CCPD has been proposed as an alternative to CAPD for all patients in whom peritoneal dialysis is appropriate (Diaz-Buxo, 1985). In patients with a strong medical or social indication for the adoption of CCPD, the benefits may be so convincing that waiting for supporting evidence from CCTs may not be justified. However, the adoption of this new

treatment modality as an option for patients who could be adequately managed by the standard treatment (CAPD) does need to be justified by evidence of clinical benefit from clinical trials. If the benefits are mainly social, relating to patient preference, patients and healthcare purchasers need to know if CCPD has any extra cost in terms of morbidity/mortality or resource use (Woodrow, *et al.*, 1994) in order to make informed decisions. However, CCPD may actually have clinical as well as psychosocial benefits; some authors have reported a reduced incidence of peritonitis with CCPD compared with CAPD (Diaz-Buxo, 1985; Brunkhorst, *et al.*, 1994).

Objective

The objective of this review is to compare CCPD with CAPD in the management of patients with ESRD. The hypotheses being tested are that, compared with patients on CAPD, those on CCPD have:

- (a) a reduced frequency of peritoneal dialysis-associated peritonitis
- (b) a reduced frequency of exit-site and tunnel infections
- (c) a reduced frequency of peritoneal dialysis catheter changes
- (d) a reduced incidence of abdominal hernias, hydrothoraces and exit-site leaks
- (e) a reduced incidence of technique failure (the need to change to other dialysis methods, such as haemodialysis)
- (f) improved blood pressure control
- (g) improved control of hyperkalaemia (a measure of dialysis adequacy)
- (h) improved adequacy of dialysis as measured by serum urea, creatinine, Kt/V and PCR
- (i) reduced rate of hospitalisation
- (j) improved patient survival
- (k) improved nutritional status (as reflected by serum albumin levels)

- (l) improved quality of life and general well-being
- (m) a preference for CCPD
- (n) similar resource use demands.

Materials and methods

Criteria for considering studies for this review

Types of studies An attempt was made to identify all trials comparing CCPD (experimental group) with CAPD (control group) in the management of patients with ESRD in which the patients were prospectively randomly (for example, using sealed envelopes with third party involvement) or quasi-randomly (alternate patients or alternate treatments) allocated to either treatment. Cross-over trials in which treatments alternated at least to the degree A–B–A–B were also to be included, even if the allocation to first treatment was neither random nor quasi-random.

Types of participants Patients with ESRD who were suitable for both CCPD or CAPD, irrespective of age, sex, race, primary renal disease or comorbidity. Trials which were exclusively comprised of patients with acute renal failure were excluded. Each individual study's definition of ESRD was accepted.

Types of intervention The experimental treatment (CCPD) comprised night-time exchanges performed by an automated cyclor machine in the patient's home. Patients may have also performed one or more daytime cycles (manually or otherwise). The control treatment (CAPD) comprised a variable number of manual peritoneal dialysis exchanges performed during the day by either the patient or an assistant. An overnight in-dwelling exchange may also have been performed. None of the control exchanges were performed by an automated cycle machine. Studies which included patients on intermittent peritoneal dialysis (peritoneal dialysis performed by an automated cyclor machine for a prolonged period two or three times per week either in hospital or in the patient's home) were excluded.

Types of outcome measures

1. Number of episodes of peritoneal dialysis-associated peritonitis
2. Number of exit-site infections
3. Number of peritoneal dialysis catheter tunnel infections
4. Number of abdominal hernias
5. Number of hydrothoraces

6. Number of episodes of exit-site leaks
7. Technique failure (the need to switch to another mode of dialysis such as haemodialysis)
8. Serum potassium (mmol/l)
9. Serum urea (mmol/l)
10. Serum creatinine ($\mu\text{mol/l}$)
11. Kt/V
12. PCR
13. Serum albumin (g/l)
14. Systolic blood pressure
15. Diastolic blood pressure
16. Mean arterial blood pressure
17. Hospitalisation (days per patient per year)
18. Measurement of quality of life
19. Patient preference (if crossover trial)
20. Employment status
21. Mortality.

Search strategy for identification of studies

The search strategy used was one developed for the identification of all possible RCTs or quasi-RCTs relating to the management of ESRD, and is described in detail in chapter 2 and appendices 2 and 3.

Methods of the review

Identified studies were evaluated using a study evaluation form and those which met the eligibility criteria (included references) were then considered in detail. Data were extracted using a data abstraction form designed for this review (see appendix 10). Review Manager v. 3.0 was used for the analysis). For a full description of the methods used, see chapter 2.

Description of studies

Only one study met the inclusion criteria (de Fijter, *et al.*, 1994); 97 unselected patients with ESRD were randomised, 47 to CCPD and 50 to CAPD. However, following withdrawals and drop-outs before commencing dialysis, only 41 patients received CCPD and 41 patients received CAPD. The study was conducted at a single centre in a university hospital setting (otherwise patients were unselected) in Amsterdam, The Netherlands. The main characteristics of the study are summarised in *Table 34*.

Methodological quality of included studies

The single study found was a randomised parallel open trial with a clear description of withdrawals and drop-outs (see *Table 34*).

TABLE 34 Characteristics of included studies: CCPD versus CAPD in treatment of patients with ESRD

Study	Method	Participants	Interventions	Outcomes	Notes
de Fijter, <i>et al.</i> , 1994	Parallel RCT; randomisation method not described; blinding not mentioned; numbers and reasons for withdrawals and drop-outs given; analysis not on intention-to-treat basis.	97 consecutive unselected new patients with ESRD; drop-outs after randomisation but before dialysis commenced resulted in 41 patients in each group; median age – CCPD, 54 years (range, 21–76 years), CAPD, 56 years (18–86 years); M:F, 52:45; no previous RRT or renal transplant; duration on RRT, first dialysis; inclusion criteria – new patients with ESRD; exclusion criteria – absolute contraindication to peritoneal dialysis; co-morbidity – “co-morbid conditions distributed equally between the two groups”.	Randomised to CCPD or CAPD; duration of study: CCPD follow-up, 723 patient months, CAPD follow-up, 688 patient months; CCPD prescription: PAC-X cycler, 4–5 nocturnal cycles, 1 diurnal cycle, 2-litre fill volume; CAPD prescription: Y-set disconnect system (no disinfectant), 2–5 2-litre exchanges daily; partner assistance not mentioned.	Infective complications: episodes of peritonitis, exit-site and tunnel infections; removal of catheter; technique survival; number of abdominal hernias, hydrothoraces; dialysis adequacy, serum creatinine, Kt/V; hospitalisation rate; quality of life, general well-being – Karnofsky score; blood pressure control, mean arterial blood pressure.	

Results

The meta-analysis of the results from the included study (de Fijter, *et al.*, 1994) are shown in *Table 35* (A and B).

Infective complications

There were no significant differences in the numbers of patients who had one or more episodes of:

- peritonitis (OR, 0.56; 95% CI, 0.24, 1.33)
- exit-site infection (OR, 1.13; 95% CI, 0.43, 2.94)
- tunnel infection (OR, 0.5; 95% CI, 0.05, 4.99).

Infective complications were also reported as episodes per patient-year. There was a significantly decreased mean incidence per patient-year of peritonitis – 0.51 (CCPD) compared with 0.94 (CAPD) ($p = 0.03$) – but no difference in the mean incidence of exit-site infection – 0.38 (CCPD) and 0.38 (CAPD).

Technique survival

Fewer patients allocated to CCPD changed mode of dialysis (excluding renal transplants and recovery of renal function but including change between the two methods of peritoneal dialysis under assessment). The OR was 0.48 but the difference was not statistically significant (95% CI, 0.18, 1.26). Similarly, fewer patients in the CCPD group switched to haemodialysis but again the difference was not statistically significant (OR, 0.46; 95% CI, 0.14, 1.56).

Seven patients on CCPD compared with 11 patients on CAPD required peritoneal dialysis catheter removal (OR, 0.57; 95% CI, 0.20, 1.61). The difference was reported as being related to infective complications.

Mechanical complications

There were equal numbers of abdominal hernias (OR, 1.0; 95% CI, 0.19, 5.22) and hydrothoraces (OR, 1.0; 95% CI, 0.06, 16.27) in both groups. Exit-site leaks were not reported.

Dialysis adequacy

There was no significant difference in Kt/V at 6 months (WMD, 0.40; 95% CI, –0.23, 1.03). This study also reported no significant difference in 6-monthly serum creatinine, urea and phosphate.

Blood pressure control

No data were presented which could be used in the meta-analyses; however, there were no significant differences in reported 6-monthly mean arterial blood pressure measurements.

Quality of life and general well-being

Patients' performance status was recorded at 6-monthly intervals using a Karnofsky score. There was no significant difference between the two groups.

Hospitalisation

Fewer patients allocated to CCPD were judged to require hospitalisation, although this was not

statistically significant (OR, 0.5; 95% CI, 0.21, 1.20). However, there was a statistically significant difference in the number of hospital admissions per patient-year of treatment (data which could not be converted into an OR) – 0.6 (CCPD) and 1.0 (CAPD) ($p = 0.02$).

Nutritional status

Data for 6-monthly serum albumin were only presented graphically and a reliable OR could not therefore be estimated. There was no significant difference between the groups.

TABLE 35A CCPD versus CAPD: overall summary

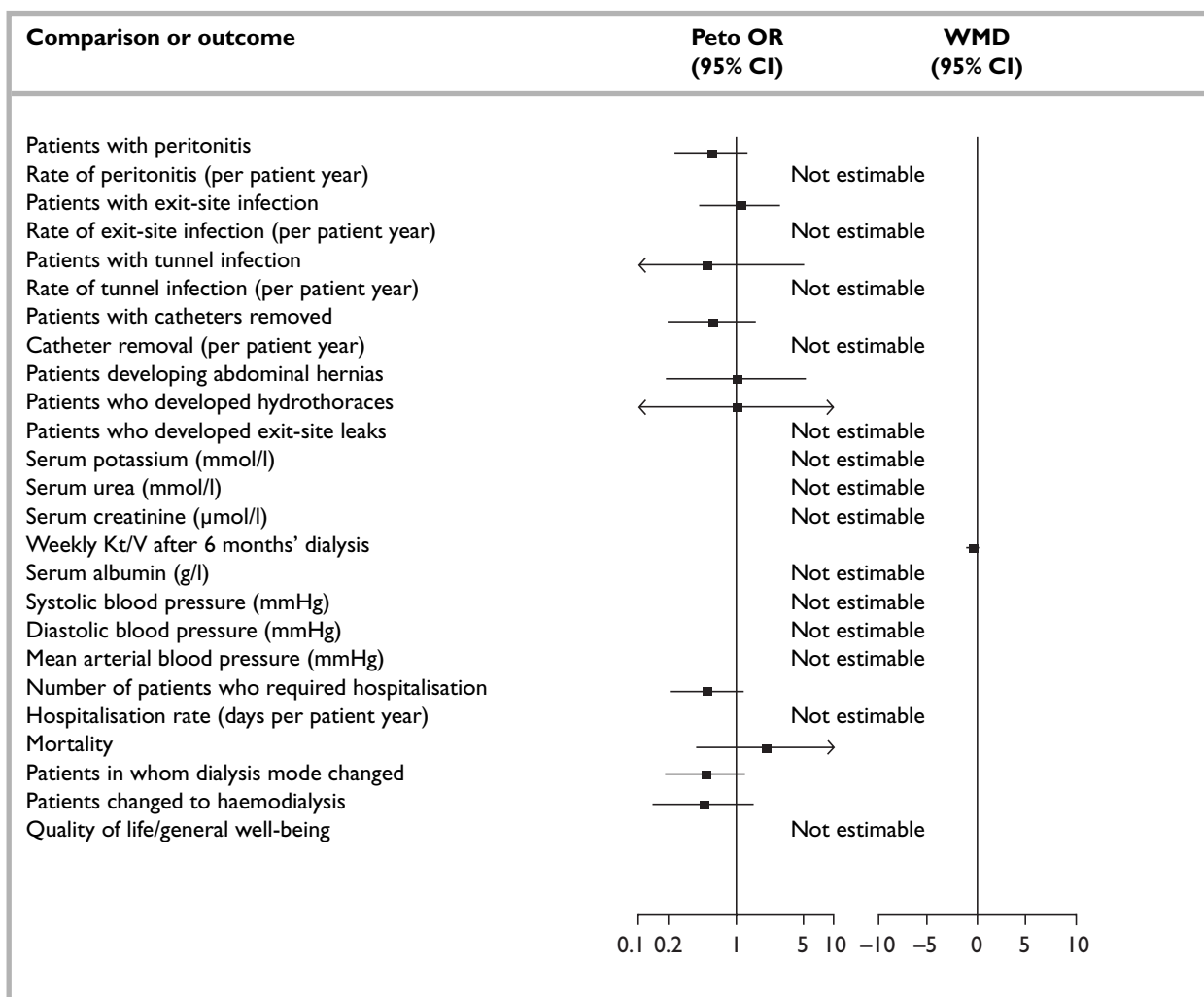


TABLE 35B CCPD versus CAPD: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Patients with peritonitis					
de Fijter, 1994	19/41	25/41		100.0	0.56 (0.24, 1.33)
Total (95% CI)	19/41	25/41		100.0	0.56 (0.24, 1.33)
Chi-square 0.00 (df = 0) Z = 1.32					

continued

TABLE 35B contd CCPD versus CAPD: detailed meta-analysis

Study	Experimental n/N	Control n/N	Peto OR (95% CI fixed)	Weight (%)	Peto OR (95% CI fixed)
Patients with exit-site infection					
de Fijter, 1994	12/41	11/41		100.0	1.13 (0.43, 2.94)
Total (95% CI) Chi-square 0.00 (df = 0) Z = 0.24	12/41	11/41		100.0	1.13 (0.43, 2.94)
Patients with tunnel infection					
de Fijter, 1994	1/41	2/41		100.0	0.50 (0.05, 4.99)
Total (95% CI) Chi-square 0.00 (df = 0) Z = 0.58	1/41	2/41		100.0	0.50 (0.05, 4.99)
Patients with catheters removed					
de Fijter, 1994	7/41	11/41		100.0	0.57 (0.20, 1.61)
Total (95% CI) Chi-square 0.00 (df = 0) Z = 1.06	7/41	11/41		100.0	0.57 (0.20, 1.61)
Patients developing abdominal hernias					
de Fijter, 1994	3/41	3/41		100.0	1.00 (0.19, 5.22)
Total (95% CI) Chi-square 0.00 (df = 0) Z = 0.00	3/41	3/41		100.0	1.00 (0.19, 5.22)
Patients who developed hydrothoraces					
de Fijter, 1994	1/41	1/41		100.0	1.00 (0.06, 16.27)
Total (95% CI) Chi-square 0.00 (df = 0) Z = 0.00	1/41	1/41		100.0	1.00 (0.06, 16.27)
<i>continued</i>					

TABLE 35B contd CCPD versus CAPD: detailed meta-analysis

Study	Experimental		Control		WMD (95% CI fixed)	Weight (%)	WMD (95% CI fixed)
	n	mean (SD)	n	mean (SD)			
Weekly Kt/V after 6 months' dialysis							
de Fijter, 1994	39	-3.40 (1.60)	39	-3.00 (1.20)		100.0	-0.400 (-1.028, 0.228)
Total (95% CI)	39		39			100.0	-0.400 (-1.028, 0.228)
Chi-square 0.00 (df = 0) Z = 1.25							
Number of patients who required hospitalisation							
de Fijter, 1994	20/41		27/41			100.0	0.50 (0.21, 1.20)
Total (95% CI)	20/41		27/41			100.0	0.50 (0.21, 1.20)
Chi-square 0.00 (df = 0) Z = 1.55							
Mortality							
de Fijter, 1994	4/41		2/41			100.0	2.04 (0.39, 10.62)
Total (95% CI)	4/41		2/41			100.0	2.04 (0.39, 10.62)
Chi-square 0.00 (df = 0) Z = 0.84							
Patients in whom dialysis mode changed							
de Fijter, 1994	8/41		14/41			100.0	0.48 (0.18, 1.26)
Total (95% CI)	8/41		14/41			100.0	0.48 (0.18, 1.26)
Chi-square 0.00 (df = 0) Z = 1.49							
Patients changed to haemodialysis							
de Fijter, 1994	4/41		8/41			100.0	0.46 (0.14, 1.56)
Total (95% CI)	4/41		8/41			100.0	0.46 (0.14, 1.56)
Chi-square 0.00 (df = 0) Z = 1.24							

Mortality

Four patients in the CCPD group died compared with two patients in the CAPD group (OR, 2.04; 95% CI, 0.39, 10.62); this was not statistically significant.

Discussion

Only one study from the 13,000 abstracts considered met the eligibility criteria for inclusion (de Fijter, *et al.*, 1994). Although this study appeared to be well conducted, its value is limited by its small sample size (82 patients in total). The results tended to favour CCPD in respect of a reduction in infective complications, reduced technique failure and reduced need for hospitalisation but none of the differences in these pre-stated measures reached conventional levels of statistical significance. When expressed as episodes per patient-year, there were statistically significantly fewer episodes of peritonitis and hospital admission. These findings increase the likelihood that the other findings reflect true differences between the techniques. Because it was a parallel study and all the patients were new to dialysis at its commencement, patient preference was not reported.

The use of CCPD as an alternative to CAPD therefore receives some support from this study. It suggests that where the option of CCPD is being offered on the basis of patient preference, convenience is not being paid for by increased morbidity and mortality. However, the capital outlay for the extra machines and the larger volume of peritoneal dialysate used makes CCPD significantly more expensive than CAPD. While controversy persists about the size of any benefits, a general change towards CCPD from CAPD for patients on chronic peritoneal dialysis is not yet warranted.

The generalisability of this review is obviously also hampered by its dependence on a single study. This was a single centre study and, although 97 patients were randomised, the predictable attrition rate from drop-outs resulted in there being only 24 patients in the final 24-month review. Further studies, preferably multicentre studies, are needed to produce more precise estimates of the differences between CCPD and CAPD suggested by this study. Peritonitis is the most frequent major complication of all forms of peritoneal dialysis. It results in significant morbidity, mortality and dialysis technique failure. If future studies confirm a significant reduction in its frequency with

CCPD, then CCPD should become the preferred option in chronic peritoneal dialysis.

Future RCTs on this topic should, like this study, concentrate on primary outcomes of major clinical importance, such as peritonitis, technique failure and mortality. The fact that none of 98 new patients with ESRD had an absolute contraindication to peritoneal dialysis counters the argument that patient numbers in RCTs comparing different modes of dialysis would be significantly limited by exclusion criteria dictated by contraindications to specific dialysis modes. CCPD should not be viewed solely as an alternative to CAPD. Although more expensive than CAPD, it may have less resource demands than hospital haemodialysis and may be a viable alternative, even when there is a relative contraindication to CAPD (for example, when significant input from a partner or assistant is required).

Economic evaluation

Introduction

The principles of economic evaluation are described in detail in chapter 3 (page 9) including, in an economic framework, the manner in which costs and outcome are related (see, in particular, *Table 2* and *Figure 3*).

Aims

CCPD is a modification of CAPD in which dialysate exchanges are automatically performed by an automated cyclor machine. It is considered that CCPD offers additional benefits over CAPD in that it provides a more acceptable lifestyle for patients and a reduced risk of peritonitis. The relative efficiency of these alternatives will be investigated using the framework of economic evaluation outlined in chapter 3. More specifically, the aims of this economic evaluation are:

- (i) to investigate the relative resources used and the cost of CCPD and CAPD using data extracted from the identified RCTs and non-randomised studies in which CCPD and CAPD are compared
- (ii) to combine data on the difference in costs with data on differential benefits to patients from the systematic review of effectiveness described above in order to assess the relative efficiency of dialysis with CCPD or CAPD.

Methods

Data collection

The methods used are described in detail in chapter 3 of the main report.

Benefits to patients

The systematic review of RCTs or quasi-RCTs described above had as its main objective the synthesis of the effectiveness data from the RCTs. Information was extracted from the RCTs on the following:

- (a) the frequency of peritoneal dialysis-associated peritonitis
- (b) the frequency of exit-site and tunnel infections
- (c) the frequency of peritoneal dialysis catheter changes
- (d) the incidence of abdominal hernias, hydrothoraces and exit-site leaks
- (e) the dialysis technique survival
- (f) blood pressure control
- (g) the control of hyperkalaemia
- (h) the adequacy of dialysis as measured by serum urea, creatinine and Kt/V
- (i) the hospitalisation rate
- (j) patient survival
- (k) patient nutritional status
- (l) patient quality of life and general well-being
- (m) patient preference for modality type.

Identification of resource use and costs

The comparison of the resources used by the two forms of peritoneal dialysis focused only on those areas where there was likely to be some difference in resource use. The identification of the relative resources used when treating patients with either CCPD or CAPD involved four steps.

1. The definition of the process of care so that all items of resource use could be identified. Different quantities of resources could potentially be consumed during the initial catheter insertion, the training process, the dialysis process (which would involve routine checks on the patients' status) and the treatment of any complications that might occur.
2. The extraction of all relevant information from the RCTs.
3. The assessment of the data on resource use contained in the studies that were not randomised.
4. The information on resource use (obtained in steps 2 and 3) could then be combined with information on the unit cost of the resources to determine the cost differential between CCPD and CAPD using the methodology described below. This differential could then be compared with data on differential benefits to patients obtained from the systematic review of effectiveness.

Model of costs

1. **Catheter insertion** Peritoneal dialysis requires a catheter to be inserted to provide access to the peritoneum. Haemodialysis may be required until peritoneal dialysis can be performed. For both types of peritoneal dialysis the process of catheter insertion is the same. Thus the resources consumed would also be the same.
2. **Training** Once the catheter is inserted a patient is trained to carry out peritoneal dialysis. This training takes several weeks and can be performed on an in- or outpatient basis. Patients may require haemodialysis during the training period. For simplicity, it has been assumed that the resources required for training are the same. This assumption is discussed below.
3. **The dialysis process** This includes the costs of capital items, consumables used, any staff inputs for the process of dialysis and the resources used during routine outpatient visits. The capital resources and consumables used were identified from de Fijter and colleagues (1994) and combined with information on prices obtained from manufacturers to obtain the cost of these items for a 1-year period. Although patients also require routine outpatient visits (information on the resources consumed and the frequency of these outpatient visits can be obtained from Coyte and colleagues (1996)), these visits were not costed as they were assumed to be identical for both CCPD and CAPD.
4. **Treatment of complications** The relative cost of treating complications associated with the different methods of peritoneal dialysis was also calculated, using the model depicted in *Figure 12* was used. If the patient does not drop out, then they return to another period of peritoneal dialysis (indicated in *Figure 12* by the movement from 'A₁' back to 'A' or 'B₁' back to 'B'). From the report by de Fijter and colleagues (1994), data were extracted on the proportion of patients who were treated for a specific complication, such as peritonitis, catheter infection or hernia, within a 1-year period. The review of the RCTs and non-randomised studies attempted to identify the precise treatment that was provided for a specific complication. These were then costed according to the staff times, consumables used, overhead costs and capital costs of the treatment. The price of any pharmaceuticals consumed was taken from the BNF (BMA, 1996) and the cost of staff time was estimated by combining information on time with that from the relevant UK NHS salary scales (NHS, 1996a; b).

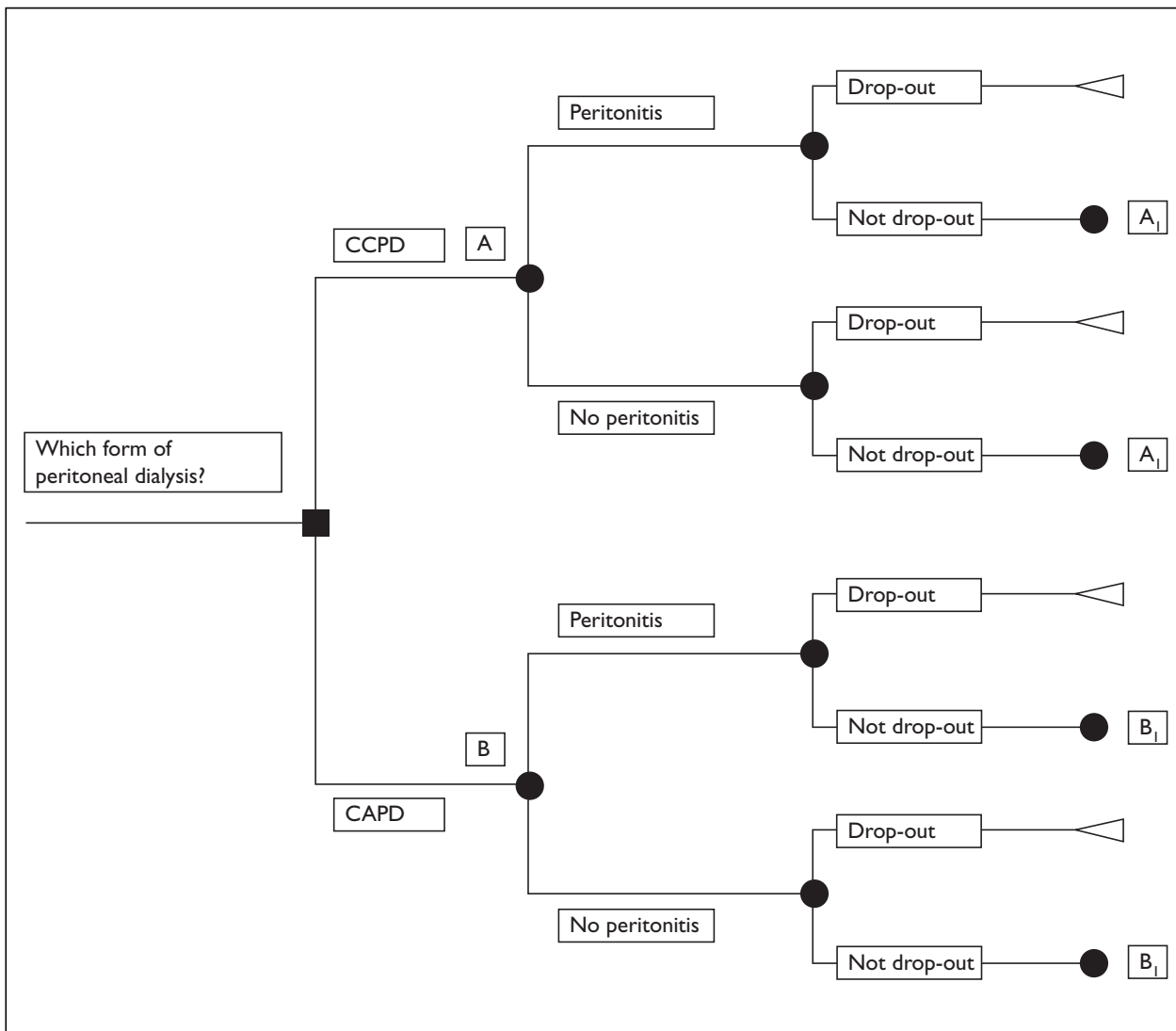


FIGURE 12 Decision model to compare the alternative forms of haemodialysis (■, decision node; ●, chance node; ◁, terminal node)

The analysis in this paper is based on intention-to-treat. The RCTs were thus reviewed in order to identify information on the proportion of patients who suffered technique failure or had renal transplants. Also recorded was the time delay to any switch in treatment.

Results

Benefits to patients

The results of the systematic review of effectiveness data were reported earlier. In brief, the systematic review identified only one RCT that met the inclusion criteria for the study (de Fijter, *et al.*, 1994). There was no significant difference in the numbers of patients receiving CAPD or CCPD who had one or more episodes of: peritonitis (OR, 0.56; 95% CI, 0.24, 1.33), exit-site infection (OR, 1.13; 95% CI, 0.43, 2.94) or tunnel infection (OR, 0.5; 95% CI, 0.05, 4.99). Infectious complications, when reported as episodes of peritonitis per patient per year,

were significantly decreased (CCPD, 0.51; CAPD, 0.94; $p = 0.03$) but there was no difference in the number of exit-site infections (CCPD, 0.38; CAPD, 0.38). There was no significant difference in the number of patients who changed mode of dialysis.

There was also no differences in the numbers of abdominal hernias and hydrothoraces. The incidence of exit-site leaks, however, was not reported. No significant differences were found between CCPD and CAPD for dialysis adequacy, blood pressure control, quality of life/general well-being, nutritional status or mortality.

There was no significant difference in the number of patients hospitalised (OR, 0.5; 95% CI, 0.21, 1.20). There was, however, a significant difference in the hospital admissions per patient-year of treatment – data which could not be calculated as an OR (CCPD, 0.6; CAPD, 1.0; $p = 0.02$).

Resource use and costs

The principle cost differences between CCPD and CAPD result from differences in the costs of the two processes of dialysis and the costs of treatment for complications.

Resources used before and during the dialysis session

It has been assumed that the resources used and the costs of the initial insertion of the catheter and of training the patient to use the designated mode of peritoneal dialysis are the same for both CCPD and CAPD.

Cost of peritoneal dialysis

The costs per patient per year for both CAPD and CCPD are shown in *Table 36*. They include the capital outlay and the consumables used in the dialysis process. The cost of routine outpatient visits has not been included as these have been assumed to be the same for patients treated by either method.

The costs are made up from the cost of the consumables used, for example, the dialysates and equipment required for exchanges, and the capital cost of the cyclor for CCPD. The current purchase price of all equipment was obtained from the manufacturers and converted into an equivalent annual cost using a 6% discount rate and assuming a life-span of 3 years. All exchanges are assumed to be performed by the patient or the patient's carer. The time that the patient or their carer spends in performing exchanges has not been estimated but is likely to differ between the two treatment modalities.

Cost of complications

The evidence presented above suggests that only the rates of peritonitis and number of hospital

admissions per patient per year are significantly different. The rates of drop-out and the reasons for drop-out for both treatment modalities are not significantly different (de Fijter, *et al.*, 1994). The cost per episode of both hospitalisation and peritonitis are shown in *Table 37*, and the probabilities that such a complication will occur are shown in *Table 38*.

Based on the model depicted in *Figure 12*, the data included in *Tables 36–38* can be used to calculate the relative cost per patient of using CCPD or CAPD for the duration that a patient can be expected to be on each treatment modality. Costs incurred after the initial year on dialysis are discounted at an annual rate of 6%.

The results using the model show that it would cost on average £22,670 to manage a patient on CCPD until treatment failure and it would cost £17,000 to manage a patient on CAPD until treatment failure (*Table 39*).

TABLE 37 Cost per episode of peritonitis and hospitalisation

Condition	Item of resource use	Cost per episode (£)
Peritonitis	10-day course of antibiotics: Vancomycin (10 vials 250 mg plus 2 × 500 mg injection)	65
	Serum concentration (one per day)	300
	Syringe	12
	Total	377
Hospitalisation	10 days per year	1993

TABLE 36 Relative costs of CCPD and CAPD

Exchanges	Item of resource use	Cost per item of resource use (£)	CCPD	CAPD
			Cost per patient per year (£)	Cost per patient per year (£)
Capital	Cyclor	7800	2918	N/A
Consumables	Tubing set (reusable as drainage bag)	12.5	4563	N/A
	Y connector	2.1	3066	3066
	Nightly exchanges	16	5840	N/A
	Daily exchanges	3.5 or 5.3	1277	7738
	Cap	0.45	164	657
	Shield	0.45		657
Labour	Time spent performing exchanges	not estimated		
Total			17,828	12,118
N/A, not applicable				

TABLE 38 The probabilities of different events for CAPD and CCPD

	Probabilities per year		Note
	CCPD	CAPD	
Training	1	1	Not included
Catheter insertion	1	1	Not included
Catheter removal	0	0	Not included
Hospital admissions per year	0.6	1	de Fijter, <i>et al.</i> , 1994
Peritonitis	0.51	0.94	de Fijter, <i>et al.</i> , 1994
Drop-out (first year)	0.73	0.73	de Fijter, <i>et al.</i> , 1994
Drop-out (subsequent)	0.4	0.4	de Fijter, <i>et al.</i> , 1994
Transfer to CAPD from CCPD		0	Simplification
Transfer to CCPD from CAPD	0		Simplification

TABLE 39 Relative cost of CCPD and CAPD per patient up to technique failure

Modality	Cost per patient (£)	Extra cost per patient of CCPD over CAPD (£)	Average period before technique failure (years)
CCPD	22,670	5670	1.22
CAPD	17,000	–	1.22

Combining costs and benefits

The combination of the information on the relative effectiveness and cost of CCPD and CAPD can provide information on their relative efficiencies. The available information on benefits suggests that CCPD provides more benefits to patients than CAPD but at greater cost. (Area C1 on the framework described in *Figure 3*). Here a judgement is required about whether the extra benefits are worth this additional cost, which requires consideration of the opportunity cost of providing CCPD instead of CAPD. (An opportunity cost is defined in terms of the benefits that could have been obtained if the resources were used in their next best alternative use.) The consequence

of using limited resources in one way is that the opportunities to use them in other desirable ways are given up. The cost of that decision is the benefit that could have been obtained by using the resources in other desirable ways.

The RCT identified in this systematic review (de Fijter, *et al.*, 1994) can be used to provide additional information to aid in the judgement between CCPD and CAPD. Using data from the RCT on the rate per patient of technique failure, peritonitis and hospitalisation, the average incidence per patient of peritonitis and hospitalisation can be calculated; the peritonitis and hospitalisation rates per patient are shown in *Table 40*.

Using the data on the additional cost of CCPD relative to CAPD (*Table 38*) and the additional benefits of CCPD (*Table 40*), it is possible to calculate the additional cost per patient per case of peritonitis or hospitalisation avoided with CCPD relative to CAPD. As shown in *Table 41*, CCPD prevents an additional case of peritonitis per patient relative to CAPD at a cost of £20,100 or CCPD prevents an additional case of hospitalisation per patient at a cost of £11,570. The issue is whether the extra

TABLE 40 Peritonitis and hospitalisation rates per patient up to technique failure

Modality	Peritonitis rates per patient	Additional rate of peritonitis of CAPD over CCPD per patient	Hospitalisation	Additional rate of hospitalisation of CAPD over CCPD per patient
CCPD	0.62	0	0.73	0
CAPD	0.89	0.27	1.22	0.49

TABLE 41 Additional cost per patient on CCPD of hospitalisation or episodes of peritonitis avoided

1	Additional cost of CCPD over CAPD	£5670
2	Number of cases of peritonitis avoided per patient on CCPD relative to CAPD	0.27
3	Extra cost per patient per case of peritonitis avoided (Row 1/ Row 2)	£21,000
4	Number of episodes of hospitalisation avoided per patient on CCPD relative to CAPD	0.49
5	Extra cost per patient per episode of hospitalisation avoided (Row 1/ Row 4)	£11,570

benefits of a case of peritonitis or the avoidance of an episode of hospitalisation are worth the additional cost, given that the additional resources could be used to achieve benefit elsewhere.

Discussion

The only study identified which met the eligibility for inclusion criteria (de Fijter, *et al.*, 1994) demonstrated significant reductions in episodes of peritonitis and hospital admissions per patient-year with CCPD compared with CAPD, and no published economic evaluations were found on this study question. There were, however, no differences in other infective complications, technique survival, mechanical complications, dialysis adequacy, blood pressure control, nutritional status, general well-being or mortality. Because it was a parallel study and all patients were new to dialysis when it started, patient preference was not reported.

The study shows that the modest additional benefits of CCPD of over CAPD are achieved at much greater cost. The question is whether these modest clinical benefits and unmeasured benefits, such as patient preference, are worth these extra resources. It is unlikely that these modest benefits would support a general change to CCPD, given that the extra resources are likely to provide much greater benefit if used elsewhere.

The strength and generalisability of this review is obviously hampered by its dependence on a single study. This was a single centre study and, although 97 patients were randomised, the predictable attrition rate from drop-outs resulted in there being only 24 patients at the final 24-month review. The incidence of many of the complications and the technique failure recorded did not significantly differ between treatments. This may have been because there was no difference or it may have

been because the study was too small to detect differences. Further studies, preferably multicentre studies, are needed to confirm and statistically strengthen the comparability of CCPD and CAPD indicated by this study. Peritonitis is the most frequent major complication of all forms of peritoneal dialysis. It can result in significant morbidity, mortality and dialysis technique failure. If future studies confirm a significant reduction in its frequency with CCPD, the extra benefits may outweigh the extra cost.

In this economic evaluation, costs are derived from estimates of resource use and probabilities which are directly taken from studies conducted in different settings; hence, the results may not be generalisable. The quantity of resources consumed in any given setting is influenced by their prices, and prices can, and do, vary between settings.

Also, the total costs of treatment with CCPD or CAPD have not been calculated. Only those areas in which there are differences in resource utilisation have been investigated. Assumptions have been made about the aspects of care that are the same for both modalities of treatment. For example, it has been assumed that the same process of care was followed for the insertion of the peritoneal catheter for both treatments.

In this situation there is no reason to believe that the process of care would be different and, hence, the assumptions that the resources used and the outcomes of insertion are the same are probably valid. Patients require training for peritoneal dialysis and this has also been assumed to be the same. In reality, patients on CCPD are likely to require training in both techniques (in case of emergencies), which patients solely on CAPD do not. However, the duration of training is unlikely to differ. The cost of training CCPD patients is likely to be slightly greater than CAPD patients and, other things being equal, this would tend to reduce the efficiency of CCPD relative to CAPD.

Future RCTs on this topic should concentrate on primary outcomes of major clinical importance such as peritonitis, technique failure, mortality and, also, strength of patient preference. The evaluation of strength of patient preference for a particular modality may highlight significant benefits of treatment not elicited through primary outcomes.

CCPD should not be viewed solely as an alternative to CAPD. Although more expensive than CAPD it may have less resource demands than hospital haemodialysis and may be a viable alternative

when there is a relative contraindication to CAPD (for example, when significant input from a partner or assistant is required).

Conclusions and implications

Policy implications

CCPD is a comparable alternative to CAPD in terms of patient outcome but is more expensive. Providers of dialysis services require to make a judgement about whether the extra cost is worth the extra benefit that it may provide.

Future research needs

1. Further RCTs are required in which CCPD is compared with CAPD with particular reference to peritonitis, technique failure rates and patient preference. If these confirm the reduced peritonitis rate of CCPD, it may need to be considered as the preferred chronic peritoneal dialysis option.
2. The more widespread use of CCPD may have significant resource-use implications. Future RCTs should include a thorough economic evaluation to provide more information on whether any additional benefits are worth the additional resources that CCPD, relative to CAPD, may require.

RCTs and economic evaluations are required that compare CCPD with haemodialysis to determine whether it is efficient to provide CCPD for those patients who have a relative contraindication to CAPD and would otherwise be treated by haemodialysis.

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Appendix 9

Systematic review 6: Comparison of haemodialysis with CAPD as treatment for patients with ESRD

Introduction

Patients with ESRD require either dialysis (haemodialysis or peritoneal dialysis) or renal transplantation to maintain life. A renal transplant is normally considered to be the preferred choice but there are insufficient donors to meet the demand. Therefore, for those patients for whom transplants are unavailable or who are not suitable for transplantation, a decision has to be made on which mode of dialysis should be used.

The objective of this review was to ascertain if there is clear evidence for the increased effectiveness of haemodialysis compared with CAPD for all patients with ESRD or for a particular sub-group. Another objective was to ascertain the relative costs of haemodialysis and CAPD, and to combine this information with the information on effectiveness to determine which method is the more efficient.

The review is described in detail in chapter 2. In addition, a systematic review of economic aspects was undertaken to identify formal economic evaluations that had tried to assess the relative efficiency of CAPD and haemodialysis.

However, as no RCTs were identified that compared CAPD with haemodialysis, only the review of economic evaluations was possible.

Economic evaluation

Introduction

The principles of economic evaluation are described in detail in chapter 3 (page 9) including, in an economic framework, the manner in which costs and outcome are related (see, in particular, *Table 2* and *Figure 3*).

Methods

Search for data on efficiency

The methods of data extraction and analysis used are described in detail in chapter 3 of the main report.

The following data were extracted from the economic evaluations identified; author, title, year of study, study question, country and setting, study design of main data source, methodological quality, (e.g. blinding, intention-to-treat) of the main data source, sample size, measures used and main findings.

Results

Identification of data on resource use and cost

The systematic literature search for studies that reported data on resource use for haemodialysis and compared CAPD was intended to identify the costs of the relative resource use of these two modes of treatment. The intention was that this information would be combined with data on benefits obtained from the systematic review of RCTs. However, since no RCTs were identified this was not possible.

It was possible, however, to systematically identify reports of economic evaluations that approximately matched the study question. Studies that did not include at least a comparison of CAPD and haemodialysis were excluded. Economic evaluation involves the formal analysis of the costs (resources use) and effectiveness (health effects) of two or more courses of action. Hence studies that only analysed the cost of these two modalities were excluded because they did not contain a formal description of the relative benefits of CAPD or haemodialysis or implicitly assumed the benefits of the two treatments were equal. When information on relative costs are not combined with benefits then there is insufficient evidence to assess the relative worth of alternative interventions under investigation. This situation is depicted by row 'D' in *Figure 3* (page 10), where the question marks indicate there is insufficient evidence.

For the same reason, studies of the costs of illness in which the global costs of the treatment of ESRD were reported were also excluded because they did not provide information on patient costs and do not report information on the relative

effectiveness of CAPD and haemodialysis. A total of seven evaluations were identified (Tajima, *et al.*, 1987; Churchill, *et al.*, 1984; Croxson & Ashton, 1990; Karlberg & Nyberg, 1995; Sesso, *et al.*, 1990; Huraib, *et al.*, 1990; Smith, *et al.*, 1989); a summary of these articles is presented in *Table 42*.

All except two of the studies (Karlberg & Nyberg, 1995; Smith, *et al.*, 1989) were based on retrospective unmatched cohort studies. Two studies addressed the efficiency of CAPD relative to hospital haemodialysis, (Karlberg & Nyberg, 1995; Huraib, *et al.*, 1990), two also looked at renal transplantation (Tajima, *et al.*, 1987; Sesso, *et al.*, 1990), two included both home haemodialysis and renal transplantation (Croxson & Ashton, 1990; Karlberg & Nyberg, 1995), and one looked at CAPD, hospital haemodialysis, home haemodialysis and subsidiary unit haemodialysis (Smith, *et al.*, 1989). The results are summarised in *Table 43*.

So far the work of Tajima and colleagues (1987) has been considered in abstract form only because the main text is in Japanese and is not yet available in translation. This study, based on a retrospective cohort of 27 patients, reported that renal transplantation was cheaper than CAPD which, in turn, was cheaper than hospital haemodialysis. Limited information on benefits was given in the abstract, reporting only that the quality of life of patients with transplants was better than the quality of life of patients on hospital haemodialysis. No information was provided in the abstract on the quality of life of patients receiving CAPD relative to hospital haemodialysis.

Churchill and colleagues' (1984) paper is based upon a retrospective cohort design comparing CAPD and hospital haemodialysis. This type of study design does not control for potential biases in patient selection. Separate data are not reported on costs but the number of life-years gained was reported to be greater for hospital haemodialysis than for CAPD (see *Table 43*). The study reported that the cost per life-year gained of CAPD versus no treatment was Canadian \$33,400 and of hospital haemodialysis was Canadian \$48,700 in the financial year 1980/81. The cost estimates used in this study are mostly based on fees and it is unclear how well these correspond to the economic or opportunity cost of providing these treatments. A further issue is that the calculation of costs and benefits is based solely on data for the 32 patients on hospital haemodialysis and 12 patients on CAPD for 1980/81. This is a small sample and the limited follow-up for this chronic condition means that important information may be missed. In particular, the complications of haemodialysis, such as access problems, and complications of CAPD other than peritonitis, such as catheter infections, are not considered. The short follow-up also means that changes in modality were also not considered.

The study by Croxson and Ashton (1990), based on a retrospective non-randomised cohort, compared four alternative modes of management of ESRD: CAPD, hospital haemodialysis, home haemodialysis and renal transplantation. This study developed a mathematical Markov process (see Glossary) based on the data from 280 patients on dialysis and on

TABLE 42 A summary of the study design and comparisons made in the identified economic evaluations comparing haemodialysis with CAPD for treatment of patients with ESRD

Study	Source of evidence	Country of origin	Comparison
Tajima, <i>et al.</i> , 1987 (abstract only)	Unmatched retrospective cohort	Japan	CAPD, hospital haemodialysis, transplantation.
Churchill, <i>et al.</i> , 1984	Unmatched retrospective cohort	Canada	CAPD, hospital haemodialysis.
Croxson & Ashton, 1990	Unmatched retrospective cohort and literature review	New Zealand	CAPD, hospital haemodialysis, home haemodialysis, transplantation
Karlberg & Nyberg, 1995	Survey of population of patients with ESRD	Sweden	CAPD, hospital haemodialysis, outpatient haemodialysis, transplantation
Sesso, <i>et al.</i> , 1990	Unmatched cohort of non-diabetic patients	Brazil	CAPD, hospital haemodialysis, transplantation
Huraib, <i>et al.</i> , 1990	Unmatched retrospective cohort	Saudi Arabia	CAPD and hospital haemodialysis
Smith, <i>et al.</i> , 1989	Matched prospective cohort	Wales	CAPD, hospital haemodialysis, home haemodialysis, subsidiary dialysis unit

TABLE 43 A summary of the results of the identified economic evaluations comparing haemodialysis with CAPD for treatment of patients with ESRD

Study	Sample size	Costs	Benefits	Cost per unit of benefit
Tajima, <i>et al.</i> , 1987 (abstract only)	27 patients	Per patient per month (yen): CAPD 3,800,000 Hospital haemodialysis 60,000 Transplant 760,000 1st month 660,000 2nd month onwards 240,000	Quality of life of transplant greater	No data reported in the abstract
Churchill, <i>et al.</i> , 1984	44 patients followed-up for 1 year; CAPD, 12, Hospital haemodialysis 32	Not reported	Survival on modality: CAPD, 12 patients each survived 8.52 years Hospital haemodialysis, 32 patients each survived 26.14 years	Cost per life-year per patient (CAN \$): CAPD, \$33,400 Hospital haemodialysis, \$48,700
Croxson & Ashton, 1990	280 patients followed-up for 5 years	Present value per patient per life-year (NZ \$): CAPD, 60,125 Hospital haemodialysis, 98,260 Home haemodialysis, 80,245 Transplant, 79,800	Present value of life-years per patient: CAPD, 2.28 Hospital haemodialysis, 2.78 Home haemodialysis, 2.85 Transplant, 4.29	Cost per life-year per patient (NZ \$): CAPD, 26,390 Hospital haemodialysis, 35,270 Home haemodialysis, 28,175 Transplant, 18,483
Karlberg & Nyberg, 1995	Swedish ESRD population – approximately 537–574 per million population	Per patient per year (\$): CAPD, 30,000 Hospital haemodialysis, 60,000 Outpatient haemodialysis, 40,000 Transplant, 10,000	All modes of treatment assumed to obtain the same survival	Cost per life-year per patient (\$): CAPD, 30,000 Hospital haemodialysis, 60,000 Outpatient haemodialysis, 40,000 Transplant, 10,000
Sesso, <i>et al.</i> , 1990	121 patients followed-up for 1 year; CAPD 24, Hospital haemodialysis 47, Transplant 50	Per cohort per year (\$): CAPD, 282,996 Hospital haemodialysis, 516,112 Transplant, 208,159	CAPD, 22.5 total years for 24 patients Hospital haemodialysis, 47 total years for 47 patients Transplant, 44.7 total years for 50 patients	Cost per life-year per patient (\$): CAPD, 12,578 Hospital haemodialysis, 10,981 Transplant, 4657
Huraib, <i>et al.</i> , 1990	58 patients, CAPD 19, Hospital haemodialysis 39	Per patient per month (Saudi Riyals): CAPD, 6534 Hospital haemodialysis, 8364	CAPD, 2/19 died at a mean of 14 months follow-up (range 3–31 months) Hospital haemodialysis, 4/38 died at a mean of 21 months follow-up (range 5.5–43 months)	Not calculated
Smith, <i>et al.</i> , 1989	127 patients, CAPD 20, Subsidiary renal unit haemodialysis 40, Hospital haemodialysis 22, Home haemodialysis 45	Per patient per year (£): CAPD, 7109 Subsidiary renal unit haemodialysis, 14,476 Hospital haemodialysis, 15,702 Home haemodialysis, 10,221	100% survival assumed per modality for 5 years. Rosser matrix health state utility: CAPD, 0.94 Subsidiary renal unit haemodialysis, 0.93 Hospital haemodialysis, 0.90 Home haemodialysis, 0.94	Cost per QALY per patient (£): CAPD, 6731 Subsidiary renal unit haemodialysis, 15,594 Hospital haemodialysis, 15,702 Home haemodialysis, 9292

data extracted from the literature. The costs per patient per year of treatment were greatest for hospital haemodialysis, followed by home haemodialysis, renal transplantation and, finally, CAPD. The study reported that the benefits to patients, calculated from the Markov model based on the retrospective cohort study, was greatest for renal transplantation, followed by, in descending order, home haemodialysis, hospital haemodialysis and CAPD (see *Table 43*). The cost per life-year gained relative to no treatment was least for renal transplantation, followed by, in ascending order, CAPD, home haemodialysis and hospital haemodialysis. The methodology used to conduct the economic evaluation was robust, since the Markov process approach allowed the transfer of patients between modalities and allowed the modelling of patient survival using the data from the cohort study. However, it only considered costs and benefits for 5 years. The authors also emphasised that there may be considerable selection bias due to the non-randomised nature of the study.

The study by Karlberg and Nyberg (1995) compared hospital haemodialysis, outpatient haemodialysis (haemodialysis under minimal supervision but still within the same hospital setting), CAPD and renal transplantation. The study purports to be a cost-effectiveness analysis. However, it explicitly assumes that survival is the same for all patients and does not consider differences in quality of life. The study is also based on unmatched cohort data and thus there may be substantial selection biases. The study reported that the costs per year was least for renal transplantation, then CAPD, followed by outpatient haemodialysis and hospital haemodialysis, respectively.

Sesso and colleagues (1990) from Brazil compared CAPD, hospital haemodialysis and renal transplantation. The benefits of treatment per patient were reported to be greatest for hospital haemodialysis, followed by CAPD and, finally, transplantation. The costs of treatment per patient were reported to be greatest for CAPD, then hospital haemodialysis and least for renal transplantation (see *Table 43*). It also found that the cost per life-year gained was least for renal transplantation, then hospital haemodialysis then CAPD. This study was based on a retrospective cohort of patients but did not allow for patients switching between modalities. The cost-effectiveness of hospital haemodialysis was heavily influenced by the low wage rates of staff and the re-use of membranes. When correction is made for the re-use of consumables for haemodialysis, it becomes more expensive per life-year than CAPD.

Huraib and colleagues (1990) from Saudi Arabia compared CAPD and hospital haemodialysis. Approximately the same percentage of patients in both arms of the study died during the study period (13% of haemodialysis patients and 11% of CAPD patients). Of the patients initially treated by CAPD, 43% transferred to another modality of dialysis and patients treated with CAPD spent more time in hospital for dialysis-related reasons (e.g. access problems, peritonitis, fluid overload) than did patients treated with haemodialysis. CAPD was associated with a reduction in the number of required transfusions and thus a reduction in the chance of transfusion related complications, such as hepatitis. The introduction of recombinant human EPO to correct the anaemia suffered by haemodialysis patients has reduced the requirements for blood transfusions in haemodialysis patients. Thus the benefits of CAPD are no longer relevant in this respect. No attempt was made to combine the alternative measures of effectiveness and so no explicit judgement was made as to whether haemodialysis was more effective than CAPD. The study also reported that CAPD was cheaper than haemodialysis; however, the costing methodology was not described and it is unclear what costs were included and whether the costing methodology made allowance of the ability of patients to switch between modalities. Furthermore, the study was based on a retrospective cohort of patients and there was differential follow-up of patients in the two groups (haemodialysis patients were followed up for a mean of 21 months and CAPD patients were followed up for a mean of 15 months).

The report to the Welsh Office by Smith and colleagues (1989) compared hospital haemodialysis, home haemodialysis, CAPD and haemodialysis at 'subsidiary' centres. This study explicitly assumed that survival was the same for all modalities. It found, however, using the Rosser matrix (Kind, *et al.*, 1982) – a method used to measure quality of life – that the quality of life of patients was greatest for patients treated by CAPD or home haemodialysis followed by, in descending order, haemodialysis at a subsidiary unit and hospital haemodialysis. The costs of treatment were least for CAPD and, in ascending order, home haemodialysis, haemodialysis at a subsidiary unit and hospital haemodialysis. The cost per quality adjusted life-year was least for CAPD, followed by, in ascending order, home haemodialysis, haemodialysis at a subsidiary unit and hospital haemodialysis. The study was based upon a prospective matched cohort of patients, where patients were matched for age, sex and risk factors. However,

the study did not allow the switching of patients between modalities and 100% 5-year survival was assumed. The Rosser matrix, used to assess quality of life, has also been criticised as not being a valid measure of this factor (Loomes & McKenzie, 1989).

These studies report that CAPD provides less benefit to patients but at less cost than hospital haemodialysis (see *Table 43*). However, in terms of the framework described in *Figure 3* (page 10), a policy of starting on haemodialysis relative to one of starting on CAPD is described by area D4, since there are no reliable estimates of effectiveness and poor estimates of cost (as the costs of treatment are partly determined by survival, the probability of switching modality and the probability that complications will occur which are also measures of effectiveness). If the assumption is made that the available evidence is valid then, in terms of *Figure 3*, a policy of starting on haemodialysis relative to one of starting on CAPD is described by area A3. Here a judgement is required as to whether the more expensive treatment (hospital haemodialysis) is worth the extra benefit that it appears to provide. Some estimate can be obtained by looking at the ratios of cost-effectiveness for the two methods of treatment. The average cost per life year saved of CAPD is lower than that for hospital haemodialysis, as can be seen from the last column of *Table 43*. This suggests that that CAPD uses less resources than hospital haemodialysis to obtain a given output, such as a life-year saved. Additional information can be obtained by looking at the incremental cost per life-year saved for haemodialysis relative to CAPD. The incremental cost per life-year saved of haemodialysis is the ratio of the extra cost of haemodialysis over CAPD divided by the extra life expectancy of haemodialysis over CAPD. Using data from Croxson and Ashton (1990) – the strongest paper in terms of its economic methodology because of its approach to modelling the costs and benefits of the modalities under consideration – the extra cost per extra life-year saved on haemodialysis relative to CAPD (the incremental cost per life-year of haemodialysis relative to CAPD) is NZ \$76,270. The comparison of this result to the average cost per life-year saved shows that the cost of additional years of life saved by haemodialysis is 2.9 times the cost of the life-year saved by CAPD relative to no treatment (NZ \$26,390 per life-year). This relative difference would persist if the costs were converted into pounds and corrected for inflation.

Discussion

As no randomised controlled comparisons of haemodialysis with CAPD were found, we

concentrated on finding reports of economic evaluations, recognising that these would incorporate assumptions about the relative clinical effectiveness of the two modalities which may be unreliable.

In the event, only seven economic evaluations were identified that attempted to answer the study question. The synthesis of these results, with the caveats alluded to above, suggest that CAPD may be more efficient than hospital haemodialysis despite assuming that it is less effective than haemodialysis.

There are reasons for treating this conclusion with caution. The evaluations were conducted in a variety of different countries and their applicability to the UK situation may, therefore, be limited. This is a consequence of local variations in clinical practice, differences in the characteristics of the samples used and differences in the unit costs of factor inputs. In the study by Sesso and colleagues (1990), for example, the cost of haemodialysis was considered to be heavily influenced by the low cost of labour and the reuse of dialysers. While reuse of dialysers is possible elsewhere, the effect of this on overall cost is uncertain and will depend upon the sterilisation process used. The use of labour is an integral and major part of hospital haemodialysis, while comprising a comparatively minor part of CAPD costs; hence, these analyses are sensitive to variations in labour costs.

Another limitation is that, with the exception of the study by Karlberg & Nyberg (1995), all of the studies identified, were based on relatively small sample sizes and the largest study explicitly assumed that survival was the same for all treatment modalities. This assumption does not correspond with the data extracted from the four studies that reported survival (Churchill, *et al.*, 1984; Croxson & Ashton, 1990; Sesso, *et al.*, 1990; Huraib, *et al.*, 1990).

The relative cost-effectiveness of CAPD versus haemodialysis; a Markov modelling approach

Since there are no RCTs that investigate the relative effectiveness of CAPD or haemodialysis, and since there are also very few economic evaluations that seek to address the question of which method of dialysis is the most efficient, a more sophisticated economic evaluation was attempted to investigate the more appropriate modality on which a patient should initiate treatment. This economic evaluation was based on an attempt

to identify systematically observational studies that addressed the study question.

Methods of analysis

The analysis was based on a Markov model; this, in simple terms, describes possible patient pathways through a given process of care, in this case a patient's lifetime on dialysis, and can be used to estimate a patient's lifetime outcomes, such as survival and cost. The Markov model was populated by data obtained from a systematic review of observational studies (no RCT addressing this question has ever been completed). It should be noted that perfect strategies to identify observational studies do not currently exist. However, this method has the potential to allow the best model to be made from the best evidence available.

The Markov model, shown in *Figure 13*, illustrates the steps that a patient commencing treatment on haemodialysis may go through. A similar model can be defined for a CAPD patient.

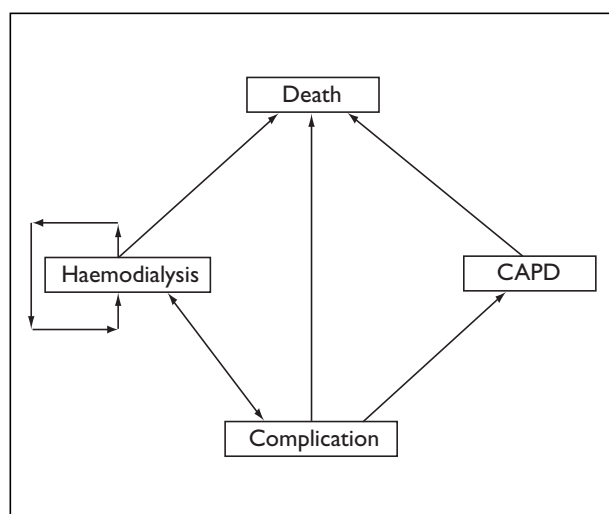


FIGURE 13 Markov model

The states of health that a patient may go through are denoted in each box. They were identified from the systematic review (Gokal, *et al.*, 1987; Charytan, *et al.*, 1986; Burton & Walls, 1989). An arrow indicates that movement from one state to another is possible. The movement between each state is determined by a probability (obtained from the systematic review) of the patient either experiencing a complication, remaining on haemodialysis or dying.

Because of the limited data available for this model, it was not possible to model a patient who switched straight to CAPD from haemodialysis without experiencing a complication first. A patient also

cannot spend more than 1 month in the state of complication.

The length of each cycle was defined as 1 month to make the model more detailed, although a patient can remain on haemodialysis, for example, for several months without experiencing a complication or dying. The patient will continue 'travelling' through this model until, eventually, the state of 'death' is reached.

The probabilities for moving between each state of health were converted to matrix form for analysis. The final analysis provided the length of time a person commencing treatment on either CAPD or haemodialysis would spend in each state of health and, hence, the total expected survival of the patient.

Costs were calculated in 1996/97 pounds sterling for each state of health within the Markov model. They included all items of resource used (e.g. labour, consumables, capital and overheads) and were based on local prices. For haemodialysis, costs were based on the patient undergoing three dialysis sessions per week; for CAPD, costs were based on four exchanges per day.

Costs were built up from one dialysis session or exchange, then aggregated to a yearly cost and divided by twelve to obtain the monthly cost. The cost of access surgery was also calculated and added to the final cost. Costs and survivals were not discounted as the Markov model does not allow for this.

Survival of patients with ESRD

Low and high estimates of survival of patients initiating treatment either on CAPD or haemodialysis are shown in *Table 44*. The high probabilities refer to high probabilities of dying, having a complication and switching modality. The low probabilities refer to low probabilities of dying, having a complication and switching modality.

Costs of patients with ESRD

The costs for each month were multiplied by the number of months spent in that state of health to obtain the cost of survival for each treatment modality (*Table 44*). The cost of each modality varies for each scenario but the initial modality of treatment is responsible for most of the cost incurred.

Cost-effectiveness

The ratios of extra cost to extra effectiveness of providing haemodialysis in preference to CAPD are shown in *Figure 14*. These ratios were calculated

TABLE 44 Survival and costs of treatment (rounded to nearest £)

Starting treatment modality	Total cost (£)	Survival (months)
Haemodialysis 1	63,370	71.51
Haemodialysis 2	73,797	78.94
Haemodialysis 3	79,478	78.94
Haemodialysis 4	68,267	71.51
CAPD A	65,061	69.1
CAPD B	67324	71.23
CAPD C	76,426	71.23
CAPD D	73,807	69.1

1 – low costs with high probabilities; cost per month: haemodialysis £868.43, haemodialysis complication £884.95, CAPD £905.19, CAPD complication £1029.28.
 2 – low costs and low probabilities; cost per month: haemodialysis £868.43, haemodialysis complication £884.95, CAPD £905.19, CAPD complication £1029.28.
 3 – high costs and low probabilities; cost per month: haemodialysis £923.03, haemodialysis complication £1188.59, CAPD £905.19, CAPD complication £1724.65.
 4 – high costs and high probabilities; cost per month: haemodialysis £923.03, haemodialysis complication £1188.59, CAPD £905.19, CAPD complication £1724.65.

using the data presented in *Table 44*. Haemodialysis is more effective and less costly than CAPD for those comparisons where no ratio is presented.

Quality of life

The impact of weighting survival by estimates of the quality of life for each health state is shown in *Table 45*. Adjusting the actual survival by the quality-of-life weighting shows the expected period

of full health that would be considered to be equal to the actual length of survival calculated by the model. For example, a weighting of 0.5 means that each month of survival predicted by the model is equivalent to 0.5 months of full health.

Discussion

The analysis provides differing results using different assumption of costs and effectiveness. For 11 of the 16 scenarios, haemodialysis would be the treatment of choice as it provides greater survival time at a low cost than CAPD.

The ratio of extra cost of haemodialysis to its extra effectiveness for the other five scenarios varies between £396 and £1596 per additional month of survival. To allow for the extra survival, however, additional funding would be required. If extra funds could not be obtained, resources would have to be obtained from elsewhere. The judgement about whether to advocate haemodialysis over CAPD in such situations would depend on what benefits could be obtained from the use of these extra resources elsewhere.

The weighting of survival by quality of life further affects the results of the analysis. This indicates that the quality of life of patients while on dialysis is an important factor that should be taken into consideration when deciding on the initial treatment. The methodology used in this paper could, if better raw data were available, be used by clinicians to help to decide how best to treat their patients.

Although the raw data used in this study is relatively poor, it is the best available. Given that judgements have to be made on the best way of treating patients with ESRD, this model could be used by policy-makers to judge resource allocation for treatment of dialysis patients.

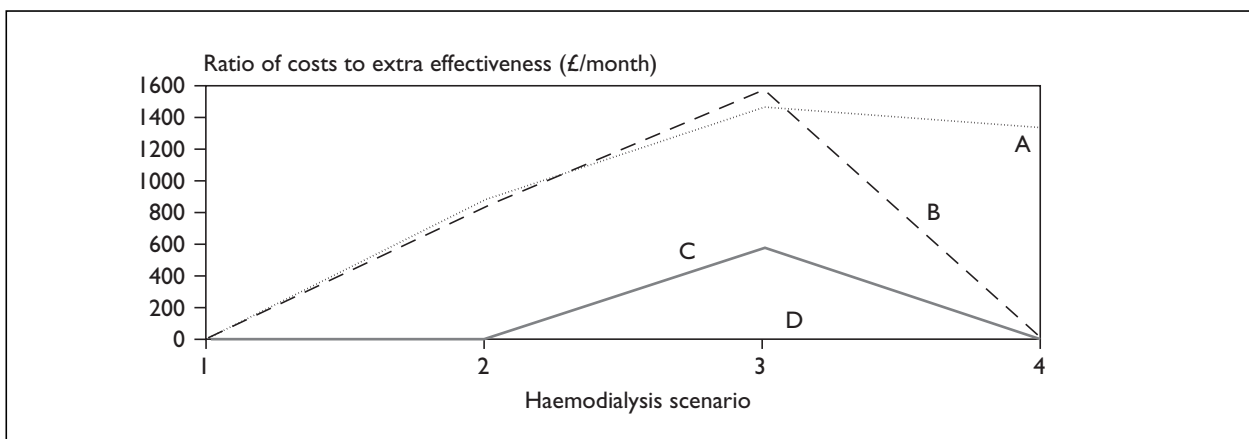


FIGURE 14 Sensitivity analysis of extra cost of haemodialysis to its extra effectiveness relative to CAPD (....., CAPD A; ---, CAPD B; —, CAPD C; —, CAPD D)

TABLE 45 Quality of life

Scenario	Quality of life weight* (assuming 1 = full health)	Quality-adjusted survival			
		Haemodialysis		CAPD	
		High (months)	Low (months)	High (months)	Low (months)
1	1, 1, 1, 1	71.51	78.94	69.10	71.23
2	0.6, 0.5, 0.6, 0.45	41.82	47.20	38.87	40.02
3	0.4, 0.2, 0.5, 0.3	26.84	31.35	31.16	32.23
4	0.8, 0.4, 0.8, 0.4	54.65	62.64	49.33	50.75
5	0.7, 0.4, 0.5, 0.3	47.86	54.80	32.05	32.65
6	0.5, 0.3, 0.7, 0.4	34.54	39.27	43.20	47.79

* Quality-of-life weights are given to each health state experienced before 'death' in the order: haemodialysis, CAPD, haemodialysis complication, CAPD complication.

The results presented here are based on the best evidence available from a systematic review. It should be noted, however, that there were only very limited data available to construct the model. Hence, the results of this study are of limited value in informing patient treatment modality. Future research should concentrate on examining the quality of life of patients on dialysis and on developing studies which provide stronger data on which a Markov model could be based.

Conclusions and implications

The issue facing the health services is not whether to have CAPD or haemodialysis but rather the balance of provision between the two modalities. It is known from variations in uptake of these techniques in different countries that a large proportion of patients requiring dialysis for ESRD could be managed with either CAPD or haemodialysis initially. What is required is information about the relative costs, benefits and risks of policies of starting with one or other treatment modality. In this respect it should be possible to develop a more detailed model based upon observational data. Ideally, information on benefits and risks should come from comparisons, within a pragmatic RCT, of policies based on starting with CAPD or haemodialysis, as used in the UK.

Data are not available to allow reliable conclusions to be drawn about the relative effectiveness and efficiency of haemodialysis and CAPD.

If an assumption is made of equal effectiveness in terms of survival then the limited data available favour CAPD.

Although some studies have assumed that a policy of starting with haemodialysis is more effective than a policy of starting with CAPD, it is not possible to quantify this extra benefit reliably using current data and, hence, it is not possible to determine whether haemodialysis is worth any extra cost that may be incurred. This issue would be resolved most reliably by a pragmatic randomised trial that included a formal economic evaluation comparing the two policies. Currently, Baxter Ltd are attempting to undertake a RCT in this area (Personal communication, 1998).

The implications of policies based on starting with haemodialysis rather than on CAPD are more complex than described in previously reported economic evaluations.

The development of new methods of dialysis, such as CCPD, and the advances in renal transplantation techniques warrant additional evaluation to investigate their place in the treatment of ESRD alongside haemodialysis and CAPD.

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Appendix 10

Forms and letters

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Randomisation form

Form sent to all authors of articles where further details of randomisation were required

NHS (UK) Executive Systematic Review of the Management of End-Stage Renal Disease

RANDOMISATION

CITATION:

1. Patients randomised to treatment groups or to order of treatment YES/NO
2. State method of randomisation used if known (e.g. day of week, date of birth, open or closed random number tables, telephone or third party involvement):

Please return to Dr Conal Daly, Department of Medicine & Therapeutics, Polwarth Building, Foresterhill, Aberdeen AB9 2ZD, Scotland.

Quality assessment form

Form completed for each article assessed for possible inclusion in any of the six reviews

Assessment of quality of trial methodology for the management of ESRD systematic reviews

Title

Journal

Year

Volume/number

Pages

Is study relevant to the management of ESRD? YES/NO

Proceed only if the answer is YES.

Which topic number?

Is study a randomised, quasi-randomised or crossover study?

YES/NO/UNCLEAR

(see accompanying notes)

Proceed only if answer is YES.

Potential for selection bias at trial entry (quality of random allocation concealment)

A = good attempt at concealment, method should not allow disclosure of assignment (telephone, third party, etc.)

B (i) = states random allocation but no description given

B (ii) = attempt at concealment but real chance of disclosure of assignment prior to formal entry (envelopes without third party involvement, random numbers table procedure not described)

C = definitely not concealed (open random numbers tables or quasi-randomised, e.g. day of week, date of birth, alternation)

Potential for selection bias in analysis

1. Was there a description of withdrawals and drop-outs?

A = States numbers and reasons for withdrawals

B (i) = States numbers of withdrawals only

B (ii) = States withdrawals but no number given

C = not mentioned

2. Numbers of withdrawals, drop-outs and those lost to follow-up for each group

3. Was the analysis on intention to treat (or is it possible to do so on available data)

A = Yes

B = Possibly, but not clear

C = No

Potential for bias around time of treatment or during outcome assessment (blinding)

1. Were patients 'blind' to treatment status (e.g. placebo)?

A (i) = action taken at blinding likely to be effective

A (ii) = blinding stated but no description given

B (i) = no mention of blinding

B (ii) = attempt at blinding but reason to think it may not have

been successful

C = not blinded

2. Were health care providers 'blind' to treatment status (e.g. placebo)?

A (i) = action taken at blinding likely to be effective

A (ii) = blinding stated but no description given

B (i) = no mention of blinding

B (ii) = attempt at blinding but reason to think it may not have

been successful

C = not blinded

3. Were outcome assessors blind to treatment status?

A (i) = action taken at blinding likely to be effective

A (ii) = blinding stated but no description given

B (i) = no mention of blinding

B (ii) = attempt at blinding but reason to think it may not have been

successful

C = not blinded

Examples of letters to biomedical companies and authors of relevant RCTs or quasi-RCTs Letter to relevant biomedical companies



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Dear [Recipient's name]

We are undertaking a systematic review of the use of acetate compared to bicarbonate buffer in the dialysate of patients with end-stage renal disease maintained on haemodialysis. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease we, in the Department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the UK. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or, alternatively, where future research should be concentrated.

Only randomised or quasi-randomised controlled clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based in Lyon, France.

[Company name] has obviously been very closely associated with research and development in haemodialysate buffer systems. We would be grateful if you could indicate if you know of any other possibly randomised or quasi-randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author).

Thank you for your time.
 Yours sincerely

Conal Daly
 Clinical Research Fellow in Nephrology

NHS (UK) Executive Systematic Review of the Management of End-stage Renal Disease Further Randomised or Quasi-randomised clinical trials

If none known please tick

If any trials known, please fill in any details available to you below.

Title	
Authors	
Department and address of institution	
Published or presented	YES/NO (please circle one)
Journal or Conference	
Volume /Number /Pages	

Title	
Authors	
Department and address of institution	
Published or presented	YES/NO (please circle one)
Journal or Conference	
Volume /Number /Pages	

Please return to: **Dr Conal Daly, Department of Medicine & Therapeutics, Polwarth Building, Foresterhill, Aberdeen AB9 2ZD, Scotland, UK.**

Letter to authors of trials where clarification of methodology required



UNIVERSITY OF ABERDEEN

DEPARTMENT OF MEDICINE AND THERAPEUTICS
POLWARTH BUILDING FORESTERHILL ABERDEEN AB9 5ZD
Telephone 01224-681616 Ext: 53073 Fax 01224-69984

Head of Department
Professor J C Petrie CBE

Dear Dr [Name]

We are undertaking a systematic review of the use of acetate compared with bicarbonate buffer in the dialysate of patients with end-stage renal disease maintained on haemodialysis. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease we in the Department of Medicine and Therapeutics at the University of Aberdeen have been commissioned to undertake by the Research and Development Programme of the National Health Service in the UK. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or, alternatively, where future research should be concentrated.

Only randomised or quasi-randomised controlled clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based in Lyon, France.

Your study: [insert title, authors] was published in [insert journal, year, volume, number and pages].

It would be very helpful if you could mark on the enclosed form whether patients in the study were randomised to different treatments or to a different order of treatment in a crossover study and what the method of random allocation used was. We would be grateful if you could also indicate if you know of any other possibly randomised or quasi-randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list – in alphabetical order according to first author). Both forms should be returned to me in the accompanying pre-paid envelope.

Thank you for your time.

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

Letter to authors of relevant RCTs or quasi-RCTs



UNIVERSITY OF ABERDEEN

DEPARTMENT OF MEDICINE AND THERAPEUTICS
POLWARTH BUILDING FORESTERHILL ABERDEEN AB9 5ZD
Telephone 01224-681616 Ext: 53073 Fax 01224-69984

Head of Department
Professor J C Petrie CBE

Dear Dr [Name]

We are undertaking a systematic review of the use of acetate compared to bicarbonate buffer in the dialysate of patients with end-stage renal disease maintained on haemodialysis. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease we in the Department of Medicine and Therapeutics at the University of Aberdeen have been commissioned to undertake by the Research and Development Programme of the National Health Service in the UK. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only randomised or quasi-randomised controlled clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based in Lyon, France.


Your study: [insert full reference including title, authors, journal, year, volume, number, pages] will be included in our review. We would be grateful if you could indicate on the enclosed form if you know of any other possibly randomised or quasi-randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list – in alphabetical order according to first author) and return it to me in the accompanying envelope.

Thank you for your time.

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

Examples of actual letters



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 POLWARTH BUILDING, FORESTERHILL, ABERDEEN AB25 2ZD
 Telephone 01224-681818 Ext: 53013/ Fax 01224-699884

Head of Department
Professor J C Petrie CBE

2 December 1996

Bradley JR, Evans DB, Gore SM and Cowley AJ
 Department of Renal Medicine
 Addenbrooke's Hospital
 Cambridge
 CB1 2QQ

Dear Doctors

We are undertaking a Systematic Literature Review of the use of Acetate compared to Bicarbonate buffer in the dialysate of patients with end-stage renal disease maintained on haemodialysis. This is one of a series of Systematic Reviews of aspects of the management of end-stage renal disease we, in the department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

Your study "Is dialysis hypotension caused by an abnormality of venous tone? British Medical Journal 1988; 296, 1634-1637" will be included in our review. We would be grateful if you could indicate on the enclosed form if you know of any other possibly Randomised or Quasi-Randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author) and return it to be in the accompanying envelope.

Thank you for your time.

Yours sincerely

Conal Daly
 Clinical Research Fellow in Nephrology

enc questionnaire on other trials
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 Telephone 01224-681818 Ext: 53013/ Fax 01224-699884

Head of Department
Professor J C Petrie CBE

2 December 1996

Abu-Hamdan DK, Desai SG, Mahajan SK, Muller BF et al.
 Medical Service
 VA Medical Centre
 Southfield and Outer Drive
 Allen Park
 MI 48101
 USA

Dear Doctors

We are undertaking a Systematic Literature Review of studies of the use of Acetate compared to Bicarbonate buffer in the dialysate of patients with end-stage renal disease maintained on haemodialysis. This is one of a series of Systematic Reviews of aspects of the management of end-stage renal disease we, in the Department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

We have identified your study "Hypoxemia during hemodialysis using acetate versus bicarbonate dialysate. Nephrol 1984; 4, 248-253" for possible inclusion in the review.

It would be very helpful if you could mark on the enclosed form whether patients in the study were randomised to different treatments or to a different order of treatment in the cross-over study and what the method of random allocation used was. We would be grateful if you could also indicate if you know of any other possibly Randomised or Quasi-Randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author). Both forms should be returned to me in the accompanying pre-paid envelope.

Thank you for your time

Yours sincerely

Conal Daly
 Clinical Research Fellow in Nephrology

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DEPARTMENT OF MEDICINE AND THERAPEUTICS
POLWARTH BUILDING, FORESTERHILL, ABERDEEN AB95 2ZD
Telephone 01224-681818 Ext. 53013/ Fax 01224-699884

Head of Department
Professor J C Petrie CBE

Albertini B, Miller J H, Gardner P W, Shinaberge J H
Department of Medicine
Wadsworth V.A Medical Centre
Los Angeles
California
USA

Dear Doctors

We are undertaking a systematic literature review of studies comparing different haemodialysis duration and frequency schedules in patients with end stage renal disease maintained on haemodialysis. This is one of a series of Systematic Reviews of aspects of the management of end-stage renal disease we, in the Department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

We have identified your study "High-flux hemodialysis under six hours/week treatment. ASAIO Transactions 1984; 33: 227-231" for possible inclusion in the review.

It would be very helpful if you could mark on the enclosed form whether patients in the study were randomised to different treatments or to a different order of treatment in the cross-over study and what the method of random allocation used was. We would be grateful if you could also indicate if you know of any other possibly Randomised or Quasi-Randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author). Both forms should be returned to me in the accompanying pre-paid envelope.

Thank you for your time

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

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Telephone 01224-681818 Ext. 53013/ Fax 01224-699884

Head of Department
Professor J C Petrie CBE

11 November, 1996

Lindsay RM, Spanner E, Heidenheim RP, Lefebvre JM, Hodsman A, Baird J, Allison MEM
Victoria Hospital
375 South Street
London
Ontario
Canada
N6A 4G5

Dear Doctors

We are undertaking a systematic literature review of studies comparing different haemodialysis duration and frequency schedules in patients with end stage renal disease maintained on haemodialysis. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease which in the department of Medicine and Therapeutics at the University of Aberdeen have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

Your study "Which comes first, Kt/V or PCR - Chicken or egg? Kidney International - Supplement 1992; S32 - S36" will be included in our review. We would be grateful if you could indicate on the enclosed form if you know of any other possibly randomised or quasi-randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author) and return it to me in the accompanying envelope.

Thank you for your time.

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

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POLWARTH BUILDING, FORESTERHILL, ABERDEEN, AB25 2ZD
Telephone: 01224-661618 Ext: 53013 Fax: 01224-669884

Head of Department
Professor J C Petrie CBE

2 December, 1996

Barbour BH, Bernstein M, Cantor PA, et al.
USC Medical School
White Memorial Medical Centre
Los Angeles
California
USA

Dear Doctors

We are undertaking a Systematic Literature Review of studies comparing biocompatible with non-biocompatible haemodialysis membranes in the haemodialysis of patients with end-stage renal disease. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease which we, in the Department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

We have identified your study, "Clinical use of NISK 440 polycarbonate membrane for hemodialysis. ASAIO, 1975; 21: 144 - 155" for possible inclusion in the review.

It would be very helpful if you could mark on the enclosed form whether patients in the study were randomised to different treatments or to a different order of treatment in the cross-over study and what the method of random allocation used was. We would be grateful if you could also indicate if you know of any other possibly Randomised or Quasi-Randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author). Both forms should be returned to me in the accompanying pre-paid envelope.

Thank you for your time

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

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POLWARTH BUILDING, FORESTERHILL, ABERDEEN, AB25 2ZD
Telephone: 01224-661618 Ext: 53013 Fax: 01224-669884

Head of Department
Professor J C Petrie CBE

6 December, 1996

Aakhus S, Bjoernstad K and Jorstad S.
Cardiology and Nephrology Section
Department of Medicine
University Hospital of Trondheim
Norway

Dear Doctors

We are undertaking a systematic literature review of studies comparing biocompatible with non-biocompatible haemodialysis membranes in the haemodialysis of patients with end-stage renal disease. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease which we, in the department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

Your study "Systemic cardiovascular response in hemodialysis without and with ultrafiltration with membranes of high and low biocompatibility. Blood Purification 1995;13:229-240" will be included in our review. We would be grateful if you could indicate on the enclosed form if you know of any other possibly randomised or quasi-randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author) and return it to me in the accompanying envelope.

Thank you for your time.

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

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Head of Department
 Professor J C Petrie CBE
 DEPARTMENT OF MEDICINE AND THERAPEUTICS
 POLWARTH BUILDING, FORESTERHILL, ABERDEEN AB95 2ZD
 Telephone 01224-681818 Ext. 53013/
 Fax 01224-698884

25 November 1996

Grefberg N
 Division of Nephrology
 Department of Internal Medicine
 University Hospital
 Uppsala
 Sweden

Dear Doctor

We are undertaking a Systematic Literature Review of studies comparing CAPD catheters - type, insertion and nursing care. This is one of a series of Systematic Reviews of aspects of the management of end-stage renal disease we, in the Department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

We have identified your study "Clinical aspects of continuous ambulatory peritoneal dialysis. *Scandinavian Journal of Urology & Nephrology Supplementum 1993 1996;72:1-46*" for possible inclusion in the review.

It would be very helpful if you could mark on the enclosed form whether patients in the study were randomised to different treatments or to a different order of treatment in the cross-over study and what the method of random allocation used was. We would be grateful if you could also indicate if you know of any other possibly Randomised or Quasi-Randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author). Both forms should be returned to me in the accompanying pre-paid envelope.

Thank you for your time

Yours sincerely

Conal Daly
 Clinical Research Fellow in Nephrology

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Head of Department
 Professor J C Petrie CBE
 DEPARTMENT OF MEDICINE AND THERAPEUTICS
 POLWARTH BUILDING, FORESTERHILL, ABERDEEN AB95 2ZD
 Telephone 01224-681818 Ext. 53013/
 Fax 01224-698884

25 November, 1996

Akyol AM, Porteous C and Brown MW.
 University Department of Surgery
 Western Infirmary
 GLASGOW
 G11 6NT

Dear Doctors

We are undertaking a systematic literature review of studies comparing CAPD catheter types, CAPD catheter insertion techniques, CAPD transfer sets and the nursing care of CAPD catheters with particular reference to prevention of CAPD peritonitis. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease which we, in the department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

Your study "A comparison of two types of catheters for continuous ambulatory peritoneal dialysis (CAPD). *Peritoneal Dialysis International 1990;10:63-66*" will be included in our review. We would be grateful if you could indicate on the enclosed form if you know of any other possibly randomised or quasi-randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author) and return it to me in the accompanying envelope.

Thank you for your time.

Yours sincerely

Conal Daly
 Clinical Research Fellow in Nephrology

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UNIVERSITY OF ABERDEEN

DEPARTMENT OF MEDICINE AND THERAPEUTICS
POLWARTH BUILDING, FORESTERHILL, ABERDEEN, AB25 2ZD
Telephone: 01224-681818 Ext: 53013 Fax: 01224-699884

Head of Department
Professor J C Petrie CBE

20 February 1997

Flanigan M, Pflederer TA, Lim VS
W346 GH
University of Iowa Hospitals and Clinics
200 Hawkins Dr
Iowa City
IA 52242
USA

Dear Doctors

We are undertaking a Systematic Literature Review of studies comparing Automated Peritoneal Dialysis with CAPD. This is one of a series of Systematic Reviews of aspects of the management of end-stage renal disease ws, in the Department of Medicine and Therapeutics at the University of Aberdeen, have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

We have identified your study "Is 8 hours of nightly peritoneal dialysis enough? *ASAIO Journal* 1994; 40: 24-26" for possible inclusion in the review.

It would be very helpful if you could mark on the enclosed form whether patients in the study were randomised to different treatments or to a different order of treatment in the cross-over study and what the method of random allocation used was. We would be grateful if you could also indicate if you know of any other possibly Randomised or Quasi-Randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author). Both forms should be returned to me in the accompanying pre-paid envelope.

Thank you for your time

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

enc questionnaire on other trials
questionnaire on randomisation
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DEPARTMENT OF MEDICINE AND THERAPEUTICS
POLWARTH BUILDING, FORESTERHILL, ABERDEEN, AB25 2ZD
Telephone: 01224-681818 Ext: 53013 Fax: 01224-699884

Head of Department
Professor J C Petrie CBE

12 November 1996

de Fijter CW, Oe PL, Nauta JJ, et al
Division of Nephrology
Free University Hospital
P.O. Box 7057
1007 MB Amsterdam
The Netherlands

Dear Doctors

We are undertaking a systematic literature review of studies comparing Automated Peritoneal Dialysis with CAPD. This is one of a series of systematic reviews of aspects of the management of end-stage renal disease which in the department of Medicine and Therapeutics at the University of Aberdeen have been commissioned to undertake by the Research and Development Programme of the National Health Service in the United Kingdom. The purpose of the project is to describe the evidence-base for certain key decisions in ESRD management and thus indicate, where possible, what is best practice or alternatively where future research should be concentrated.

Only Randomised or Quasi-Randomised Controlled Clinical trials will be included in our review. The methodology of our literature search and trial assessment is based on that of the Cochrane Collaboration. We are members of the nascent Renal Cochrane Group based at Lyon, France.

Your study "A prospective, randomized study comparing the peritonitis incidence of CAPD and Y-connector (CAPD-Y) with continuous cyclic peritoneal dialysis (CCPD). Advances in Peritoneal Dialysis 1991; 7: 186-189" will be included in our review. We would be grateful if you could indicate on the enclosed form if you know of any other possibly randomised or quasi-randomised studies published, unpublished or in progress on this topic in addition to those we have already identified (see enclosed list in alphabetical order according to first author) and return it to me in the accompanying envelope.

Thank you for your time.

Yours sincerely

Conal Daly
Clinical Research Fellow in Nephrology

enc questionnaire on other trials
list of trials
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Data abstraction form for systematic review of membranes used in chronic haemodialysis					
Reference:					
Characteristics of participants					
Characteristic	Overall	Synthetic	Cellulose	Mod cellulose	Notes
Study population					
Age (mean, range & SD or SEM)					
Male:Female					
Co-morbidity description					
Inclusion criteria					
Exclusion criteria					
Characteristics of intervention					
Duration of trial i.e. how long with each membrane					
Duration/frequency of dialysis					
Vascular access					
Blood flow rate					
Dialysate flow rate					
Buffer type acetate/bicarbonate					
Membrane detailed name flux complement activation surface area					
EPO (yes/no)					
ACE inhibitor (yes/no)					
Reuse/no. of times					

Data abstraction form for systematic review of membranes used in chronic haemodialysis continued					
Reference:					
Outcome measures					
Outcome measure	Synthetic	Cellulose	Mod cellulose	Notes	
Symptomatic hypotension or hypotension requiring treatment (episodes, patients or treatment sessions)					
Intradialytic headaches					
Intradialytic nausea & vomiting					
Intradialytic pruritus					
Intradialytic – any adverse symptoms					
General well-being/ quality of life					
Number of episodes of significant infection					
Predialysis albumen					
PCR					
Adequacy Kt/V URR					
Mortality					
No. of hospital admissions & length of stay					
No. episodes of anaphylaxis					
Predialysis beta 2 microglobulin					
Fasting predialysis total cholesterol					
HDL cholesterol					
LDL cholesterol					
Triglyceride					

Data abstraction form for systematic reviews of acetate vs. bicarbonate buffer in haemodialysis

Reference:

Characteristics of participants

Characteristic	Overall	Acetate	Bicarbonate	Notes
Study population				
Age (mean, range)				
Male:Female				
Reduced muscle mass				
Cardiovascular status				
Liver disease				
Other co-morbidity				
Prior "acetate intolerance"				
Inclusion criteria				
Exclusion criteria				

Characteristics of intervention

Duration of trial				
Duration/frequency of dialysis				
Blood flow rate				
Dialysate flow rate				
Dialyser type				
Membrane type				
Membrane surface area				
Dialysate osmolality				
Dialysate sodium conc.				
Dialysate buffer conc.				
Ultrafiltration rate				
Antihypertensive use				

Data abstraction form for systematic reviews of acetate vs. bicarbonate buffer in haemodialysis continued

Reference:

Outcome measures

Outcome measure	Acetate	Bicarbonate	Notes
Symptomatology (intra-, post- and interdialytic) and interventions necessary			
Patient acceptability			
Quality of life improvement			
Headache			
Nausea/vomiting			
Muscle cramps			
Anorexia			
Weight (gain/loss)			
Indices of nutritional assessment			
Symptomatic hypotension			
Non-specific intolerance			
EEG changes			
Dialysis dysequilibrium			
Anti-emetic			
Crystalloid/colloid			
Postural change			
Quinine/other intervention for muscle cramps			
Analgesia			
Discontinuation of dialysis session (temporary/permanent)			
Physician requested to see			
Hospital admission (duration and location)			

Data abstraction form for systematic reviews of acetate vs. bicarbonate buffer in haemodialysis continued				
Reference:				
Outcome measures continued				
Outcome measure	Acetate	Bicarbonate	Notes	
Parameters of cardiovascular stability/instability				
Hypotension				
Left ventricular function/cardiac output				
Peripheral vascular resistance				
Right heart pressure values				
ECG changes				
Pulse rate				
Parameters of renal bone disease				
Symptoms				
Parathyroid hormone level				
Serum calcium				
Serum phosphate				
Alkaline phosphatase				
Radiological evidence of renal bone disease				
Histological evidence of renal bone disease				
Lipid profile				
Serum cholesterol				
Serum triglycerides				

Data abstraction form for systematic reviews of acetate vs. bicarbonate buffer in haemodialysis continued				
Reference:				
Outcome measures continued				
Outcome measure	Acetate	Bicarbonate	Notes	
Acid-base balance				
Arterial pH				
Arterial Po ₂				
Arterial PCO ₂				
Arterial standard bicarbonate				
Arterial base excess				
Respiratory rate				
Tidal volume				
Other pulmonary function tests				
Measures of dialysis adequacy				
Serum potassium				
Serum urea (include URR)				
Other measure of dialysis adequacy				
Trialists conclusions:				

Data abstraction form for systematic review comparing short duration haemodialysis treatments with standard duration treatments			
Study:			
Characteristics of participants			
	Short duration dialysis	Standard duration dialysis	Notes
Number of patients			
Age (mean, sd)			
Male:female			
Duration on RRT			
Residual renal function			
Co-morbidity			
Exclusion criteria			
Inclusion criteria			
Characteristics of intervention			
Duration of treatment (prescribed/achieved)			
Dialysis frequency per week			
Duration of study			
Dialyser type			
Dialysis membrane size			
Dialysis membrane type (flux, efficiency, biocompatibility)			
Dialysate flow rate			
Blood flow rate			
Ultrafiltration (litres per dialysis treatment)			
Volumetric control (yes/no)			
Dialysate composition			
Sodium concentration			
Buffer concentration			
Osmolality			
Dialyser reuse			

Data abstraction form for systematic review comparing short duration haemodialysis treatments with standard duration treatments continued			
Study:			
Characteristics of outcomes			
	Short duration dialysis	Standard duration dialysis	Notes
Mortality			
Intradialytic morbidity (number of patients, treatments, adverse symptoms)			
Headaches			
Nausea/vomiting			
Symptomatic or treatment requiring hypotension			
Muscle cramps			
Non-specifically unwell			
Interdialytic morbidity			
Pre-dialysis blood pressure			
Systolic			
Diastolic			
Mean arterial			
Hospitalisation (all cause) (number of patients, number of episodes, number of days)			
Dialysis adequacy			
Kt/V (prescribed/achieved)			
Time-averaged concentration of urea			
URR			
PCR			
Phosphate clearance			
Resource use data			

Data abstraction form for systematic review of CAPD transfer sets		
Reference:		
Characteristics of participants		
Overall	Notes	Study population
Age (mean, range, SD, SEM)		
Male:female		
Co-morbidity		
Inclusion criteria		
Exclusion criteria		
Characteristics of intervention		
CAPD catheter type		
CAPD catheter number		
Duration on CAPD (total)		
Duration with this specific catheter		
Prophylactic antibiotics at insertion (yes/no)		
Early or delayed initiation		
Long term exit-site dressings (yes/no)		
Topical Rx to exit site		
Disinfectant/antiseptic (yes/no)		
Antibiotic (yes/no)		
Which antiseptic used at exchanges?		

Data abstraction form for systematic review of CAPD transfer sets					
Reference:					
Characteristics of intervention continued					
	Overall	Double-cuffed tenchoff	Any other CAPD catheter	Notes	
Comparison with description					
Characteristics of outcome measures					
Technique survival time no. of patients					
Exit-site infections episodes patients					
Tunnel infections episodes patients					
CAPD peritonitis episodes patients					
Comparison with description	Overall	Prophylactic antibiotics (systemic) at insertion	None/placebo	Notes	
Characteristics of outcome measures					
Technique survival time no. of patients					
Infections exit-site episodes patients					
Tunnel infections episodes patients					
CAPD peritonitis episodes patients					

Data abstraction form for systematic review of CAPD transfer sets continued					
Reference:					
Characteristics of intervention continued					
	Overall	Topical disinfectant/antiseptic/antibiotic to exit-site long term	None/placebo	Notes	
Comparison with description					
Characteristics of outcome measures					
Technique survival time no. of patients					
Infections exit-site episodes patients					
Tunnel infections episodes patients					
CAPD peritonitis episodes patients					
	Overall	Antiseptic 1 used at exchanges	Antiseptic 2 used at exchanges	Notes	
Comparison with description					
Characteristics of outcome measures					
Technique survival time no. of patients					
Infections exit-site episodes patients					
Tunnel infections episodes patients					
CAPD peritonitis episodes patients					

Data abstraction form for systematic review of CAPD transfer sets continued					
Reference:					
Characteristics of intervention continued					
	Overall	Delayed CAPD initiation	Early CAPD initiation	Notes	
Comparison with description					
Characteristics of outcome measures					
Technique survival time no. of patients					
Infections exit-site episodes patients					
Tunnel infections episodes patients					
CAPD peritonitis episodes patients					
CAPD leak episodes patients					
	Overall	Long-term exit-site dressing	None	Notes	
Comparison with description					
Characteristics of outcome measures					
Technique survival time no. of patients					
Infections exit-site episodes patients					
Tunnel infections episodes patients					
CAPD peritonitis episodes patients					

Data abstraction form for systematic review of CAPD transfer sets continued

Reference:

Characteristics of intervention continued

	Overall	Modified Y-transfer set	Y-transfer set (or with different modification)	Notes
Comparison with description				
Characteristics of outcome measures				
Technique survival time no. of patients				
Infections exit-site episodes patients				
Tunnel infections episodes patients				
CAPD peritonitis episodes patients				

Data abstraction form for systematic review comparing CCPD with CAPD in the management of patients with ESRD

Types of participants

	CCPD	CAPD	Notes
Number of patients			
Age (mean, SD)			
Male:female			
Previous RRT/Tx			
Duration on RRT			
Co-morbidity			
Exclusion criteria			
Inclusion criteria			
Types of intervention			
Dialysis prescription			
Transfer set and disconnect device			
Partner assistance (yes/no)			
APD machine			
Types of outcome			
Number of episodes of peritonitis			
Number of exit-site infections			
Number of tunnel infections			
Number of catheter replacements			
Technique survival			
Number of abdominal hernias			
Number of hydrothoraces			
Number of exit-site leaks			
Serum potassium (mmol/l; mean, SD)			
Serum urea (mmol/l; mean, SD)			
Serum creatinine (µmol/l; mean, SD)			
PCR			
Kt/V			
Serum albumin (g/l)			
Systolic BP (mean, SD)			
Diastolic BP (mean, SD)			
Mean arterial BP (mean, SD)			
Hospitalisations Number Days			
Quality-of-life measurements			
Patient preference			
Employment status			
Number of deaths			



HTA panel membership

This report was identified as a priority by the Acute Sector Panel.

Acute Sector Panel

Chair: Professor John Farndon, University of Bristol †

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