THE EVIDENCE BASE

for the
National Service Framework
for Renal Services

Modules One and Two:
Dialysis and Transplantation
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INTRODUCTION

This report was commissioned by the Policy Research Programme of the Department of Health.

How we undertook the review of evidence

This report is the result of reviewing the evidence for Modules One and Two of the National Service Framework for Renal Services. These modules cover dialysis and transplantation. Questions were derived from the work of the External Reference Group and, following discussions with the York Centre for Reviews and Dissemination, search strategies were developed to address these questions. The abstracts of the publications generated by the search strategies were reviewed by the staff in York and full copies of relevant publications obtained. Certain of the studies were then excluded because of their methodology or because, despite being identified by the literature search, they did not address the subject of the question. Data were then extracted from the included studies and the data extraction tables, along with the original publications, were sent to the Evidential team who had expertise in nephrology and in reviewing literature systematically. Having read both the data extraction tables and the publications, the Evidential team produced a report for each question. The report comprised comments on the evidence, summary statements of the evidence, and a list of references for the included and excluded studies. Summary statements were given a level of evidence as described in the table below. The reports for two questions (numbers 6 and 10) included summaries of small sections of the Renal Association standards document, Treatment of adults and children with renal failure; Standards & Audit Measures, 3rd Edition. The reports were then sent to the Department of Health to aid the development of the National Service Framework. In addition, the Evidential group compiled benchmarking data on acceptance and prevalence rates for renal replacement therapy in several countries.

Levels of Evidence

Level 1: Meta-analyses, systematic reviews of randomised controlled trials, or randomised controlled trials.

Level 2: Systematic reviews of case-control or cohort studies, or case-control or cohort studies.

Level 3: Non-analytic studies, eg case reports, case series.

Level 4: Expert opinion (in the absence of any of the above). This includes the views and experiences of people with renal failure and their carers.

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Dr Kannaiyan S Rabindranath was supported by the National Kidney Research Fund (UK).
Despite rising patient numbers and increased investment, treatment rates in England are lower than those in other parts of Europe, including the rest of the UK.

The table below presents data for the number of people per million population (pmp) accepted for renal replacement therapy (RRT) - incidence - and the total number on RRT - prevalence - in 2001, for which data is available to make comparisons between England, other parts of the UK, and further afield. These rates are not however adjusted for age, co-morbidity or ethnicity.

<table>
<thead>
<tr>
<th>Country</th>
<th>New patients starting treatment (pmp)</th>
<th>Prevalence Rate (pmp)</th>
<th>Source</th>
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<tr>
<td>United States</td>
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<td>(a)</td>
</tr>
<tr>
<td>Japan</td>
<td>252</td>
<td>1624</td>
<td>(a)</td>
</tr>
<tr>
<td>Spain (Catalonia)</td>
<td>146</td>
<td>1022</td>
<td>(b)</td>
</tr>
<tr>
<td>Germany</td>
<td>184</td>
<td>919</td>
<td>(c)</td>
</tr>
<tr>
<td>Belgium (Dutch speaking)</td>
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<td>855</td>
<td>(b)</td>
</tr>
<tr>
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<td>138</td>
<td>679</td>
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<td>(b)</td>
</tr>
<tr>
<td>England</td>
<td>91*</td>
<td>547*</td>
<td>(c)</td>
</tr>
</tbody>
</table>

US Renal Data Service  
European Renal Registry  
UK Renal Registry  
ANZ Data  
(e) QuaSi-Niere  
(f) Scottish Renal Registry (2002 Scottish Renal Registry Report #2001 data)  
(g) Italian registry of Dialysis and Transplantation (RIDT)  
* Estimate calculated from 2002 UK Renal Registry Report
MODULE ONE QUESTIONS: DIALYSIS

Question 1

Has education and information given to patients with chronic renal disease at all stages in the patient pathway been shown to improve outcomes?

Comments on the evidence

Sixteen papers were reviewed, nine were excluded, either because they did not address the issue or the study design was seriously flawed. One was a randomised controlled trial (RCT) but in general the overall quality of the studies was low with many biases. The studies predominantly concerned patients approaching end-stage/established renal failure (ERF) or those on dialysis. There were no studies on transplant patients. Although none of the studies was from the UK, over half were from North America (1, 4, 5, 6) and the rest from other European countries (3, 2); the results are probably relevant to UK patients. It was difficult to disentangle the effect of the staff support received by many patients as a result of taking part in the educational programmes from the effects of the programmes themselves. In addition in some studies it was not clear whether the group who did not undergo the education programme had not wished to take part or whether they presented too late to be able to take part (5, 7). In many studies patients were allowed to choose whether they underwent the educational programme or not. This would tend to select out those with greater motivation and possibly better general health and less co-morbidity and hence likely to have better outcomes.

Summary statements

- Education of patients with progressive renal failure or ERF improved their knowledge of that disease and of renal replacement therapy. (Level 1) (2, 1)
- Patients who chose or were selected to undergo an education programme had improved psychosocial outcomes, a shorter hospital admission at the time of starting dialysis and short-term (up to six months but not thereafter) improvement in mood, mobility and decreased anxiety (one study, however, included a degree of psychological support). (Level 2). (6, 3)

References

Included studies


Excluded studies

Question 2

Has education and information given to patients with chronic disease been shown to improve outcomes?

Comments on the evidence

The evidence source available to the team was *The Expert Patient: a new approach to chronic disease management for the 21st century* (Department of Health, UK 2001); there was no formal literature search. The self-management programmes described for arthritis, manic depression and multiple sclerosis showed tangible benefits including reduced severity of symptoms, significant decrease in pain, improved life control and activity, improved resourcefulness and life satisfaction and improved communication with physicians and other health care providers. We should note that such programmes had a considerable supportive as well as educational content.

Summary statements

- Education and information given to patients with chronic disease can improve physical, mental and social outcomes. (Level 2 - may be Level 1 as is ongoing RCT in manic depression).
- Chronic renal failure affects relatively few people when compared with other chronic diseases and hence it is harder to carry out sufficiently large studies to give significant results. It may be appropriate therefore (cautiously) to extrapolate the results from other chronic disease groups. (Level 4)

Reference

Question 3

Have advice, support and counselling (eg by social workers, psychologists and specialist nurses) improved outcomes (eg access to benefits such as attendance allowance)?

Comments on the evidence

Five studies were reviewed and all were included. None were from the UK, four from the USA (1, 2, 4, 5) and one was a joint publication from the US and Germany (3). One well conducted RCT (3) (follow-up 1-5 yrs) of over 400 patients approaching dialysis who had intensive support (and almost certainly education) at clinics from physicians, nurses, dieticians and social workers showed no difference in rate of decline of renal function, survival or drug use but had a substantially increased cost – principally because of the high number of clinic visits. Outcome measures such as Quality of Life, patient satisfaction, depression scores or financial benefits received might have been of value, but the researchers were trying to determine whether increased staff input at an early stage would save resources later. The other studies, all on dialysis patients, were less robust methodologically. One is mentioned in Question 1 above (4), two others showed associations of support with an increased ability to maintain employment (education included) and a lower depression score (1, 5). A further study was a survey asking patients which professionals they had found most helpful and these were, in order; nurses, doctors, social workers, dieticians (2).

Summary statements

- Patients on dialysis find health professionals, particularly nursing staff, to be a major source of support. (Level 3) (2)
- Support and education may permit patients to maintain employment. (Level 3) (5)
- Social support may have psychosocial benefits and may allow patients to ward off the depressive symptoms that can arise in those undergoing chronic dialysis. (Level 2) (1, 4)
- The only RCT found showed no clinical benefit and increased cost for a policy of intense intervention by a multidisciplinary team before dialysis is required. (Level 1) (3)

References

Included studies

Question 4

Are there improved outcomes for patients with chronic renal failure (including dialysis and transplant) when given dietary advice?

Comments on the evidence

In many dialysis patients restriction of potassium, sodium, phosphate, and sometimes protein in the diet is required in addition to dialysis to maintain blood chemistry, and this needs to be explained to the patient. Fourteen studies on dietary advice were analysed; four were excluded for methodological reasons. Two concerned transplanted patients (5, 6), six HD patients (2, 1, 3, 7, 9, 10), two studied patients approaching dialysis (4, 8). Three studies were from the UK (1, 2, 6), one from the rest of Europe (8) and six from North America (3, 4, 5, 7, 9, 10). Dietary intervention also formed part of the RCT mentioned in Question 3 (4). Studies were generally small. In mild chronic renal failure teamwork between the physician, dietician and patient may help adherence to a low protein diet (8). In haemodialysis patients little difference was seen in compliance or biochemical values (although follow-up was short) following dietetic advice (3). One study showed improvement in albumin after an intervention that allowed patients practical help with cooking and shopping rather than just dietary advice (7). Dietary advice had a small effect on decreasing lipids in transplanted patients, but statins were more effective (5).

There was only one study which showed that staff involvement helped adherence to the diet (8). For patients on dialysis it is likely that the dialysis process has the major effect on the blood chemistry and hence the more dialysis the less the need for dietary restriction. Two of the studies (2, 1) showed the importance of fluid restriction. For most patients there is almost always some need for specific food and fluid restriction, which someone needs to explain to the patient. The effect of staff input on compliance is difficult to show.

Summary statements

• Fluid restriction advice improved weight gain between dialysis sessions. (Level 2) (2, 1)
• In progressive renal failure dietary advice and support can help a patient adhere to a low protein diet. (Level 2) (8)
• There is little and inconclusive evidence to show the effect of dietary advice on outcomes.

References

Included studies


Excluded studies


Question 5

What formal assessment criteria should be used to assess a patient for the different modalities of RRT and is there any evidence relating to improved outcomes?

Comments on the evidence

The original search generated 209 references; 13 papers were ordered for further appraisal and none deemed eligible for inclusion. One paper was excluded as it was only a brief overview of the topic (11), two were excluded as they dealt only with patients’ views (6, 12), two as they dealt only with education (8, 9), six as they did not deal with the assessment criteria (7, 10, 13, 14, 17, 18). Five further studies were found which were of peripheral interest. Three described well planned studies with similar methodology comprised of questionnaires sent to nephrologists in USA, Canada and UK (5, 4, 3) surveying their views on which factors influence dialysis modality selection – patient preference came top in all three countries but the uptake of the modalities varied (13%, 34%, 40% - for peritoneal dialysis) and what was said to the patient about the forms of dialysis was not stated. The other papers are descriptions of what the authors felt were an appropriate assessment for suitability for transplantation and what patients and staff felt were the important factors in the selection of dialysis modality.

Summary statement

- It is not clear which of the available dialysis modalities is the most effective either overall or in specific patient subgroups, nor is there a consensus on how to select patients for transplantation. At present the focus should be on equity of access to assessment for all forms of treatment for each patient and it is suggested that a consensus view on assessment criteria for transplantation be established. Research on appropriate criteria should be encouraged.

References

Included studies

2. Groome PA, Hutchison TA, Pritchard SS. ESRD treatment modality selection: which factors are important in the decision? Advances in Peritoneal Dialysis 1991; 7: 54-56

Excluded studies

6. Breckenridge DM. Patient’s perceptions of why, how and by whom dialysis treatment modality was chosen. Anna Journal 1997; 24(3): 313-19
Question 6

What is the evidence that starting dialysis early is beneficial?

Comments on the evidence

Patients reach the need for dialysis by two main routes:

- by presenting as an acute uraemic emergency, when dialysis is mandatory and planning impossible. This may occur on a background of known impaired renal function with no previous history.
- with known progressive renal impairment which has been present for many months or years. Dialysis can be planned for this second group of patients and there is controversy over when precisely such patients should begin dialysis. Much of the evidence on this is discussed in the Renal Association publication, *Treatment of adults and children with renal failure: Standards and audit measures, 3rd Edition*, page 129 paragraphs 10.21 to 10.29. (This document is available on the website www.renal.org and the principal points are noted in ‘A’ below.)

A. Bonomini reported that early commencement of dialysis, at a GFR in excess of 10 ml/min, was associated with increased survival on dialysis when compared either with historical controls who had started dialysis only when they developed symptoms, or with patients who had commenced dialysis as an emergency (2-9). Because lead-time bias and case mix differences were not taken into account a causal relationship cannot be inferred. An attempt was made to undertake a cost-effectiveness analysis, but again without correction for case-mix biases (5). Ratcliffe (23) also reported an association between poor outcomes and late referral but included in the ‘late referral group’ patients who presented late to the medical services and hence could not have been referred earlier. Other authors made similar analyses and conclusions, without adding to our understanding of when to start dialysis (1, 12, 13, 14, 16, 17, 24). Kjellstrand (18) analysed European and American data and showed that 90% of the variation in mortality in patients on dialysis reflected comorbidity. He could find no major beneficial effect of early commencement of dialysis.

The United States Renal Data System (USRDS) data on all patients commencing dialysis has been analysed with respect to the relationship between starting serum creatinine concentration and survival on dialysis. The relative risk of mortality on dialysis rose sharply as the serum creatinine at the start of dialysis fell. The relative risk of death was 1.71 in those with a serum creatinine of <4mg/dl (<352µmol/l) at start of dialysis, 1.58 with creatinine 4-7.9mg/dl (350-700µmmol/l) and 1.2 with creatinine 8-9.9mg/dl (700-880µmmol/l). On the other hand, those with a serum creatinine >18mg/dl (>1584µmmol/l) had a mortality equal to those starting either with a creatinine of 10-11.9mg/dl (880-1050µmmol/l) or 12-17.9mg/dl (1050-1580µmmol/l).

B. A literature search of publications was carried out since those used in the Renal Association document. Six further papers were found, one of which was excluded because of methodological issues. A study from the Dutch ‘NECOSAD’ study showed that the quality of life of those who had an elective early start for dialysis was higher for certain dimensions although the effect was gone by a year (19). Recent US guidelines (DOQI) suggested that dialysis should begin when a nutritional index (nPNA) falls below a certain figure. They indicate that this is likely to happen when renal function falls below a given value and hence preserving nutrition is one reason for starting dialysis early. A further study by the NECOSAD group (15) showed, however, that good nutrition was maintained in the Dutch patients below the given value for renal function in the guidelines from the United States. A study in Scotland (25) followed patients with a glomerular filtration rate of at least 20mls per minute in order to assess the impact of early dialysis. Survival from this clearance to death was compared between those who started early (creatinine clearance greater than 8.3 ml per minute) and those who started late (less than 8.3 ml per minute). Survival was superior in late starters when assessed from a clearance of 20ml per minute. This suggests that longer survival after dialysis in early starters is at least in part due to lead time bias. This was therefore similar to the results in the NECOSAD study.

A further study currently planned (21) may help address this issue. This prospective randomised controlled study of elderly patients will randomise them when their residual renal function has reached a given value (glomerular filtration rate 5-7ml per minute) Starting dialysis at this point will be compared with a very low protein diet without dialysis. Dialysis will be commenced when it is thought clinically
It is unclear whether starting dialysis early gives improved outcomes. Considerable evidence has been accumulated to suggest that the beneficial effect may represent lead time bias. In addition some of the studies which showed that an early start was beneficial included patients who presented late, often as emergencies whose prognosis is worse because of that.

Quality of life at the time of starting dialysis is higher in those who have had an 'early start' but this effect is gone by a year. This could have been affected by lead time bias. (Level 2) (19)

An observational study has shown that adhesion to a strict very low protein diet in the elderly can postpone dialysis while maintaining good nutrition. (Level 2) (10)

A prospective randomised multi-centre trial in the elderly is planned to compare starting dialysis with supplemented very low protein diet. (21)

References

Included studies


Excluded study

**Question 7**

Does starting dialysis with permanent vascular or peritoneal access in place improve outcomes?

**Comments on the evidence**

Patients require access to the bloodstream for dialysis; this can be permanent, or temporary via a venous catheter. For peritoneal dialysis a catheter is inserted into the abdomen. It is generally thought that having permanent access available at the start of dialysis gives a patient better outcomes.

Ten studies were considered eligible for inclusion. Six studies were from North America (1, 3, 5, 7, 8, 10), one from the UK (9), two were from the rest of Europe (2, 4) and one was from Brazil (6).

Thirty five publications were excluded either because they did not address the issue in question (12, 13, 15 - 19, 21 - 26, 28, 29, 31 - 33, 35 - 39, 41 - 45) or because they were review articles (11, 14, 20, 27, 30, 34, 40).

Permanent vascular access has been taken here to mean arteriovenous fistulae (AVF) and grafts made from artificial fibres eg PTFE. ‘Permanent’ catheters (permcaths) are often used while awaiting (sometimes for many months) surgery for AVF or graft and are seen as a less good form of permanent access. Temporary catheters are used when patients present as emergencies needing urgent dialysis, and these can sometimes be left in until permanent vascular access is surgically formed, which may be for several weeks or months. A major issue in the UK is lack of access to surgical time delaying permanent access formation.

There were no RCTs. This question does not easily lend itself to RCT as permanent vascular access is so firmly believed to result in fewer complications and a higher delivered dialysis dose. One French study however gave a group of patients a permanent catheter for 12 months then an AVF for 12 months and showed a very low infection rate and a remarkably small reduction in dialysis dose, although they did have to increase the length of some of the patients’ dialysis sessions (2).

The other studies are prone to biases as they included patients who presented late who are known to have more comorbidity and less good outcomes, and as a result of their late presentation are much less likely to have permanent access. It may be also that those patients who do present early and dialyse using catheters do so because they have more comorbidity and hence vascular access is difficult to make successfully. Six out of 11 studies were from the USA (1,3, 5, 7, 8, 42), where a higher proportion of patients have grafts as permanent access compared with fistulae. One study in the elderly showed improved patency in the group with permanent catheters (7). In general however dialysis with temporary and permanent catheters were shown to result in less favourable outcomes. Some studies did not distinguish between permanent and temporary catheters (4, 5).

**Summary statements**

- Temporary catheters result in higher infection rates and hospitalisation days and have a shorter lifespan than AVFs. (Level 2) (3, 4, 6)
- Permcaths have a shorter lifespan than AVFs. (Level 2) (7, 8, 9)
- Overall patients with catheters have a higher mortality. This may reflect their late presentation and greater comorbidity but the effect was shown in studies which attempted to correct for case-mix. (Level 2) (5, 6)
- Patency of AVFs was higher at one-year follow up (8) although one study in the USA in the elderly (>69yrs) showed better patency with permcaths. (7) (Level 2)
- In general a higher delivered dialysis dose is achieved with permanent vascular access (1, 2). One study showed that this could be minimised by increasing dialysis time. (Level 2)

**References**

**Included studies**


Excluded studies


22. Chesser AM, Baker LR. Temporary vascular access for first dialysis is common, undesirable and usually avoidable. Clinical Nephrology 1999; 51(4): 228-32


31. Ifudu O, Mayers JD, Matthew JJ, Fowler A, Freidman EA. Haemodialysis dose is independent of type of surgically created vascular access. Nephrology Dialysis Transplantation 1998; 13(9): 2311-16
Question 8

Does monitoring arteriovenous fistulae or grafts prolong their life?

Comments on the evidence

Permanent access is the patient’s ‘lifeline’ on dialysis. It may be monitored clinically or by various X ray or scanning tests.

Six studies were included. Four were from the USA (1, 2, 5, 6), one from Canada (4) and one from the UK (3). Although none of the studies had access survival as an outcome measure, all examined thrombosis (clotting) or stenosis (narrowing) rates and some evaluated the effect of corrective surgery. One study estimated cost savings of the monitoring programme (2). In general in the USA compared with the UK a high proportion of patients have grafts rather than fistulae as their form of vascular access. In addition in the USA short high flux dialysis which requires a high flow rate is much more common than in the UK.

The UK study (3) had no control group but showed that of the 17 patients with reduced thrill or pulsation at the fistula (fifteen) or graft (two) (flow < 200 ml/min or venous pressure > 150mHg) who had Digital Subtraction fistulograms, 10 required revision surgery and 16/17 were using the same access at six months. Two studies of grafts carried out in the USA showed monitoring successfully identified stenosis and thrombosis, allowed their treatment and resulted in a lower thrombosis rate (1, 6). One suggested a cost saving. A further US study showed a reduction in thromboses of grafts but not fistulae as a result of ultrasound monitoring but not venous pressure monitoring (2). It also showed cost savings. A further randomised study (5) showed monitoring (either venous pressure or ultrasound) decreased thrombosis rate (fistulae) and increased patency rates (grafts and fistulae). This was a small study and they had to combine two intervention groups to get significant differences. The Canadian study had no control group and like the UK study showed that monitoring was successful in detecting stenoses in the patients monitored.

A total of 37 studies were excluded either because they were trials that did not address the issue in question (8, 10, 11, 13 - 18, 20 - 33, 35 - 38, 41 - 45, 48, 50, 52, 53) or because they were review articles (9, 12, 19, 34, 39, 40, 47, 49, 51).

Summary statements

- Monitoring of grafts can decrease thrombosis rates. (Level 2) (1, 2, 4, 5, 6)
- Monitoring of grafts may save money. (Level 2) (2)
- Monitoring can improve identification of stenoses in fistulae but studies included no control group and no economic analysis. (Level 2) (2, 3, 4, 5)

References

Included studies


Excluded studies


11. Chand DH, Poe SA, Strife CF. Venous pressure monitoring does not accurately predict access failure in children. Pediatric Nephrology 2001; 17(9): 765-69


50. Vermeij CG, Smit FW, Elsman BHP. Inability to monitor polyurethane hemodialysis vascular access graft by Doppler ultrasound. Nephrology Dialysis Transplantation 2001; 16(5): 1089-90


Question 9

What is the infection rate for permanent (cuffed) lines (used with the intention of providing long-term access) and how long do they last?

Comments on the evidence

Twelve papers were found, of which eight were excluded. Two were excluded as they studied permanent lines inserted for temporary usage (9, 13), two as they dealt only with temporary lines (10, 12), two as they did not specify whether the lines were temporary or permanent lines (14, 16), one as it had insufficient numbers of episodes of line placement (11) and one was excluded as it had insufficient event numbers (15). The four included papers were combined with the relevant ones from Question 7 (1, 2, 3, 5). Out of the nine included papers, one was from Macedonia (4), two were from France (1, 8), one from the UK (5) and four from the USA (2, 3, 6, 7).

Catheter survival was described in different ways - mean survival in days, survival at six months, 12 months etc. or as number of days the catheter survived per number of days at risk. Similarly infection rates were described differently. One study that prospectively analysed 42 patients who started dialysis with a tunnelled catheter for 12 months followed by arterio-venous access for the next 12 months (1) showed that only three out of 42 catheters required replacement because of infection. One study assessed the impact of dialysis access on the survival of elderly patients (2) and showed that in elderly dialysis patients, permanent lines were associated with the least number of additional interventions and best patient survival. A comparison of various dialysis access methods showed that permanent lines had a 9% primary patency at one year (3). One retrospective study in the paediatric dialysis population showed that the median survival for permanent lines was 195 days. One study looking at the use of various forms of haemodialysis access in Macedonia (4) showed that 11% of permanent lines were associated with infection. This study also showed that 8.9% of the lines were patent six to 12 months after insertion and 7.5% after one year. A retrospective analysis from the USA (6) showed that the infection rate was 1.67 per 1000 catheter days. This study however had only 18 patients. The 1-year access survival in that study was 47%. A nationwide surveillance of hemodialysis associated infections from the USA (7) showed that access related bacteraemia was 4.84 per 100 patient-months for permanent lines compared to 0.25 for AV fistulas and 0.53 per 100 patient-months for AV grafts. One study (8) showed that the 1-year survival of permanent lines was about 50%. There were no infectious complications in this study. The nurses in this study followed a rigorous infection prevention protocol and the patients were also educated about aseptic precautions.

Summary statements

- Survival of permcaths is variable and the 1-year survival ranges from 7.5% to 50%. (Level 2) (3, 4, 6, 8)
- Permanent lines are associated with a definite risk of infection. (Level 2) (4, 7)
- Following rigorous aseptic precautions by the dialysis unit staff and patient education regarding proper care of lines may reduce the risk of infections greatly. (Level 2) (8)
- Permanent lines are associated with less additional procedures and better patient survival in the elderly when compared with arterio-venous fistulas and grafts. (Level 3) (2)
- Overall there may be a place for permcaths in the elderly where other forms of access are difficult to insert, and possibly also in children. (Level 2) (2, 5)

References

Included studies


Excluded studies

Question 10

What is the evidence for some of the principal clinical standards in dialysis for established/end stage renal failure (ERF)?


Comments on the evidence

Water quality. There are British Standards developed from international standards for water quality for dialysis. If haemodiafiltration and haemofiltration are used, more stringent limits in respect of bacterial contamination are mandatory.

Anaemia. Patients with ERF are frequently anaemic. One of the major reasons for this is the lack of production of the hormone erythropoietin naturally formed by the normal kidney. Recombinant human erythropoietin can be produced and its advent in the 1980s revolutionised the treatment of renal anaemia. Current evidence from randomised controlled trials (level 1) of dialysis patients supports a correction of haemoglobin to between 9.5-11g/dl and currently the Clinical Standard recommended by the Renal association is >10g/dl (level 1). One large trial which included only patients with cardio-vascular disease was not completed because of the higher death rate in the group where an attempt was made to normalise haemoglobin above 12g/dl. There were some problems however with the data obtained, and further randomised controlled trials are awaited to determine whether further improvements in physical and psychological functions may be obtained with normalisation of haemoglobin in some patient groups. It may be for example in the future that haemoglobin targets should be tailored to the individual, rather than aiming for a single target haemoglobin for all patients in a dialysis unit. A proportion of patients, particularly those on peritoneal dialysis and those not yet requiring dialysis, may not need erythropoietin to obtain the target haemoglobin particularly if they are well nourished, iron replete and well dialysed.

Haemodialysis Adequacy. Dialysis adequacy is a global concept which includes clinical assessment of well being, the impact on the patient’s life, and measures of the molecular clearance by the dialysis process. The molecular weights of the solvent and solutes to be cleared by dialysis range from small (water, urea) to large (beta-2-microglobulin). Adequate clearance of the whole range of molecules by dialysis is important. For practical reasons haemodialysis adequacy is calculated using small, easily measured solutes such as urea. The urea reduction ratio (URR) is the simplest measure. It is the percentage fall in blood urea effected by a dialysis session. Adequacy can also be measured using the formula (Kt/V urea) which can be estimated from data on the pre- and post-dialysis urea concentrations, the duration of dialysis and the weight loss during dialysis. Another measure, urea kinetic modelling, which requires more comprehensive information and a computer programme, can also be used to calculate dialysis adequacy. For patients receiving thrice weekly haemodialysis level 2 evidence shows that the urea reduction ratio (URR) should be consistently greater that 65% or the equilibrated Kt/V should be greater that 1.2 (level 2). These are generally regarded as minimum standards.

Peritoneal Dialysis - Peritonitis. The major risk with peritoneal dialysis is the development of infection within the peritoneal fluid called peritonitis. It has been shown that using ‘Disconnect Systems’ reduces the risk of peritonitis (level 1). The disconnect system is a type of peritoneal dialysis equipment where the dialysis fluid bag and tube are disconnected from the peritoneal dialysis catheter after each peritoneal dialysis fluid exchange. Peritonitis rates have improved with the introduction of disconnect systems. There is mounting evidence that repeated attacks of peritonitis are associated with earlier failure of the peritoneal membrane and for this reason peritonitis rates should be kept at less than one episode for every 18 patient months for adults. (level 1).

Reference

Question 11

Does being cared for in dedicated renal wards (as opposed to being an ‘outlier’ on another ward) improve outcomes?

Comments on the evidence

There was no evidence found for the question.

General comments

- Patients with ERF undergoing either haemodialysis or peritoneal dialysis often have several co-morbid illnesses and are increasingly elderly. They therefore require relatively frequent hospital admissions with intercurrent problems.
- Where possible such patients are admitted to nephrology wards with nurses trained in renal medicine. That ward itself may provide dialysis facilities, or these may be provided in the dialysis unit, usually situated nearby.
- As the number of patients being treated for ERF increases and they become increasingly elderly and have a high number of co-morbid conditions, the requirement for inpatient admission is becoming greater. There may be insufficient renal beds and such patients, although under the care of a nephrologist, maybe in an outlying ward as a ‘boarder’ or ‘outlier’, where the nursing staff are unlikely to have had renal training. Staff on such wards will be less familiar with the care of patients who pass no urine and hence require fluid restriction, and who also have dietary restrictions, most importantly potassium restriction. Because medical staff visit from a distant ward the quality and efficiency of the medical service in addition to the nursing service is diminished.

References

None quoted
Question 12

Does being cared for in an inpatient environment with trained renal staff improve outcomes for patients on RRT?

Comments on the evidence

Eight papers were excluded as they did not address the issue in question (2 - 9). One paper was identified concerning this topic as part of the search for economic studies (1). It was from the USA and describes the difference in length of stay and cost of admission for patients admitted under the care of a nephrologist or under the care of a general physician. At the time of this study some specialist medical services were open to patient admissions on alternate days only. General medical services admitted speciality patients on the days that the speciality services were closed for admission. Thus an alternate day admission programme was in place. Length of stay and hence cost was significantly less for the patients admitted under the care of a nephrologist despite the fact that the patients admitted were older. The readmission rate was no different between the two groups. There was no difference in the number of investigations ordered or in procedures carried out or treatments given. The reasons put forward for the decreased length of admission were that the nephrologists had seen the patients on their thrice weekly visits and hence were more familiar with them and could start tests prior to admission. Likewise they could discharge the patient earlier knowing that they could continue their management as an outpatient. A further reason for the difference was thought to be the inefficiency of the consultative process, ie the time taken to notify the nephrologist that the patient was in hospital under the care of the general physician, and the time lag in carrying out the instructions of the visiting nephrologist. The author further felt that the training and experience of the nephrologist may add to the speed of diagnosis and treatment.

Summary statements

- There is some evidence from the USA to suggest that for those patients with established/end stage renal disease requiring inpatient hospital admission, their length of stay when admitted under a nephrologist is shorter that when admitted under the care of a general physician.
- Although length of admission was shorter there was no increased necessity for readmission.
- The reasons for the shorter length of stay were thought to have been:
  - the ability of the nephrologist to start investigation prior to admission and continue investigation and treatment after discharge,
  - the inefficiency of the consultative process ie in getting expert nephrology care to the patient under the care of the general physician
  - the specialised training and experience of the nephrologist.
- No evidence was found concerning the role of nurses or other staff.

References

Included study


Excluded studies

5. Luker KA, Box D. The response of nurses towards the management and teaching of patients on continuous ambulatory peritoneal dialysis (CAPD). International Journal of Nursing Studies 1986; 23(1): 51-59
**Question 13**

What does the literature say about transport of patients on haemodialysis?

**Comments on the evidence**

A total of nine papers were retrieved for appraisal and four of them were excluded as they were not relevant to the issue in question.

Chronic haemodialysis patients are disproportionately dependent on hospital transport services as they have to travel three to four times a week to the dialysis unit, and this can be time consuming and arduous especially if they live far away from the dialysis centres. The time and costs associated with hospital transport are major areas of concern. A Spanish study found that transport costs accounted for almost 16% of the entire haemodialysis provision cost (3). A study from Scotland showed that 19% of haemodialysis patients travelled in excess of 100 miles per dialysis day (15,000 miles/year) (1). Patient attitudes may be affected by the time and effort involved in transport and from the hospital. One study from Northern Ireland (5) found that because of the effort involved in travelling to the regional dialysis unit, one-third of patients receiving treatment twice a week said they would not attend more frequently even if advised to do so by the clinician. In the same study travel times were shorter for patients attending a satellite unit and they were prepared to attend more frequently if advised to do so (5). The same study showed that the main quality criterion was ‘leaving home promptly’. One study from the USA showed that introduction of a van (driven by appropriately selected and trained staff) that collected and transported patients to the dialysis unit resulted in far fewer ‘no shows’ and reduction in associated costs, and thereby contributed to more efficient use of the dialysis facility (2). A Canadian study showed that satellite units were associated with lower travel costs and resulted in a mean saving of $12,364 per patient, emphasising the cost importance of decreased travelling times (4).

The time spent in travelling to the unit as well as the time involved in waiting for a vehicle to transport patients back to their home significantly affects the time patients can spend in social activities and with their own family. Good transport facilities improve the likelihood of patient attendance and hence better utilisation of the dialysis facility. The above facts illustrate the need for a well-organised transport system for dialysis patients.

**Summary statements**

- Patient transport is particularly important to patients on haemodialysis and plays a vital role in the formation of patient views and attitudes towards dialysis. (Level 3) (1)
- Good transport systems may improve patient attendance. (Level 3) (2)
- Shorter travel times may improve patient compliance if the dialysis treatment frequency needs to be increased. (Level 3) (5)
- Transport costs contribute 16% of overall dialysis costs. (3)
- Satellite units may not only be convenient for the patient to attend but also cut transport costs. (Level 3) (4)

**References**

**Included studies**

4. Soroka SD, Kiberd BA, Jacobs P. The marginal cost of satellite versus in-centre hemodialysis. Meeting of the American Society of Nephrology, Philadelphia PA, USA, October 30-November 4, 2002; Journal of American Society of Nephrology 2002; 13(Program and Abstracts Issue: 401A

Excluded studies

Question 14

Does automated peritoneal dialysis (APD) or continuous cycling peritoneal dialysis (CCPD) have advantages compared with continuous ambulatory peritoneal dialysis (CAPD)?

Comments on the evidence

Thirty-four studies were eligible for inclusion. Only two were randomised studies (5, 3) of 82 and 34 patients respectively. One was a systematic review (15 - of RCTs that included only study number 5). The others were observational, many of which like the RCTs were small. One of the RCTs (5) showed a significant reduction in peritonitis rates in patients receiving CCPD compared with those undergoing CAPD using the ‘y-set’ system. Three of the observational studies also showed a significant decrease in peritonitis with CCPD (14, 19, 25). Two found no difference (9, 10), and two found decreased incidence with CAPD (6, 2). Bias may account for the heterogeneous results in the non-randomised studies. There is some evidence, therefore, from the small RCT that peritonitis may be less using CCPD.

Neither of the RCTs (5, 3) showed any difference in adequacy achieved when CCPD and ‘y-set’ CAPD were compared, although this was not the prime comparison of either of the studies. The non-randomised studies were small, and gave conflicting results. Three (1, 7, 11) reported no difference and five indicated that APD delivered better adequacy than CAPD (20, 21, 4, 18, 14). Four studies investigated the effects of PD on quality of life (3, 24, 16, 23). One (3) was a small RCT which found those on APD had more time for work, social and family life, but had more problems sleeping; APD took place overnight. Furthermore, nine patients withdrew from the study resulting in only 25 of them completing it. In advance, all patients had expressed a preference for APD. One of the non-randomised studies (24) showed that one of the SF36 domains (social functioning) was significantly better in those undergoing APD; there was no difference in the other seven domains. Another study showed no difference in quality of life (23), and a very small study in children (16) found CCPD was more disruptive to family life because of the anxieties associated with operating a machine and the lack of its mobility; new, smaller and simpler machines, however, may overcome these problems.

Studies of growth and nutrition were broadly inconclusive. Two non-randomised studies in children suggested it was better with CAPD (12, 22) than CCPD.

Summary statements

- There is a lack of large studies of alternative forms of peritoneal dialysis.
- There is possibly a decrease in peritonitis with APD (3). (Level 1 - but small study)
- Variable effects on quality of life (24, 16, 23), growth (12, 22) and nutrition (1, 8) (Level 3)
- There is one small study which showed patients preferred APD (3). (Level 3)

References

MODULE TWO QUESTIONS: TRANSPLANTATION

Question 15

Does having a national helpline on living related donation improve relatives’ experience and/or increase donation rate?

Comments on the evidence

Of the thirty-three papers reviewed, nine were deemed eligible for inclusion. None of the papers related to transplantation, nor indeed to any other aspect of established/end stage renal failure care. Five papers were from the UK (1, 2, 4, 9). The nation wide survey of the Coronary Heart Disease Helpline in the UK (5) showed that only 18% of the callers felt the present levels of information in that area (excluding the Helpline) were adequate, and the authors also suggest that the callers perceived health professionals as not easily accessible. The survey also showed that despite the extensive health information and promotional activities in this area of medicine, many people needed clarification of the most basic facts. A study of the UK Asthma Helpline (3) showed that the key areas of need for information were medication (85%) and side effects of medication (37%). The majority of callers (95%) felt that the information they received from the Asthma Helpline was pitched at the right level. Out of the 532 questionnaires sent out by the Dutch Cancer Information Helpline, 37% of the responders were relatives/friends (4). This study also showed that relatives/friends were more likely to ask questions regarding the psychosocial aspects of the disease.

Summary statements

• Patients have gaps in basic knowledge with respect to health related problems despite information provision. (level 3) (5, 3)
• Patients and relatives find helplines very useful in giving information in a way that they can understand. (level 3) (3)
• It is possible, therefore, that both potential donors and recipients would find a helpline useful in providing factual information, and also, perhaps, in providing counselling for the physical and psychological aspects of transplantation, both before and after any operation.

References

Question 16

Does having access to counselling improve the experience of the transplant process and outcomes of potential living donors (including those later found to be unsuitable) and recipients?

Comments on the Evidence

Of the 128 papers ordered only 13 were deemed eligible for inclusion. Two described the same study (9, 10), ten were from the USA (1 - 4, 6, 8 - 10, 12,13) one from Iran (11), one from UK (7) and one from Spain (5). They concerned three groups of patients:

1. In patients on the waiting list for renal transplantation, no effect on ‘hope’ scores or ‘uncertainty’ scores was made by giving information and support in the form of telephone calls and mailings (8).

2. For those contemplating donating a kidney there was some weak evidence to show that education in the form of a video improved living donation rates. One study was very small indeed, about 45 potential living donors (3), and the other used historical controls (9), ie the introduction of the video was associated with an increase in the living related transplant rate in the centre; but it was not clear what other differences existed around that time. This might be an important area for investigation, as a video could be made and tested in a randomised trial both for the effectiveness of understanding of a potential donor and the subsequent donation rate.

3. Patients who had already received a transplant were investigated in the majority of studies selected. Several studies showed that educational programmes improved knowledge, particularly of immunosuppressive therapy (6, 4, 13, 12, 11). As in module one (dialysis) it was very difficult to show any clinical effects. For example, it was not possible to show any improvement in drug compliance among children (1, 4) nor in hospitalisation rates or telephone contact rates (6) in those who had and had not received education programmes. Education programmes were shown to have prevented weight gain in transplants (7), decreased the cardiovascular risk factors (2) and prevented urinary tract infections (5). None of these three studies was a randomised trial.

In general, therefore, the quality of the studies was poor and the numbers within them low. None of them tested the living donors’ or indeed the recipients’ experience of the transplant process.

Summary statements

- Education improves renal transplants recipients’ knowledge of their anti rejection drugs. (Level 3) (6, 4, 13, 12, 11)
- Education improves weight gain, cardiovascular risk factors and the incidence of urinary tract infections in the post transplant patient. (Level 3) (7, 2, 5)
- Transplant recipients who have received dietary advice had decreased weight gain; those who had received advice on cardiovascular risk factors had lower cholesterol levels, and those with recurrent urinary tract infections who had received advice had, subsequently, lower rates of infection. (Level 3) (7, 2, 5)
- No studies were found that addressed the issue of counselling and education affecting outcomes of potential living donors.
- Very tentative evidence suggests that certain types of education programme may improve living donation rates. (Level 3) (3, 9)

References

Question 17

Does follow up of living kidney donors avert long term complications?

Comments on the evidence

This begs the question ‘Are there long term complications of donation in living kidney donors?’ Most of the evidence from the first literature search focused on studies in which the donors had had regular follow up and not on those who had been reviewed at a given time point after donating the kidney. Three of the major studies in which that had been done, at least 20 years after donor nephrectomy, were subsequently reviewed.

Five included studies from the first search (1, 2, 3, 6, 8) followed a total of 276 patients from between 1 and 8½ years after the kidney donation. Immediate and long term surgical complications were documented; the more long term of these were incisional hernia, keloid scar formation, lumbar pain and depression. Although 1 and 8½ years is not particularly long, none of the studies showed an increase in blood pressure nor a deterioration in renal function compared with that immediately post nephrectomy. Almost all the studies reported the development of proteinuria. There is evidence from the general literature that proteinuria in patients with renal disease can be a poor prognostic sign, but the relevance of proteinuria in someone who does not have renal disease is unclear. None of the studies comprised a randomised comparison between follow up and non-follow up; all patients had been followed up.

Two studies, carried out in the USA (4 and 7), studied long term outcomes. One showed that 5.6% of the 314 living related donor studies had developed hypertension between 0 and 14 years after the operation. Najarian’s study in 1992 is better methodologically as the prevalence of hypertension in the donors was compared with their siblings. This is sensible as in an ageing population a certain proportion will become hypertensive. There was no difference between hypertension in the siblings who had and had not given the kidneys.

A further Swedish study of 389 donors (78 >20 years before) showed a lower mortality than the general population and no deterioration in renal function (5); 20% of those who donated over 20 years before had hypertension, although this was not compared with the prevalence in an age matched population.

Overall, therefore, so few complications have been identified that a comparison of follow up versus non-follow up cannot be made.

The only benefit of life long follow up might therefore be psychological reassurance for the donor, and it might make them feel they are valued and have not been forgotten after their generous gift. There is no evidence, however, to support this.

Summary statements

- There is no good evidence for the development of hypertension or of progressively diminishing kidney function in living related kidney donors up to 20 years post donation; survival is not diminished. Proteinuria does occur and has been noted in many studies, but does not appear to be detrimental. (Level 3) (1, 7, 8, 6)
- Since a kidney is being removed for the purposes of donation and not to benefit the donor, it may be that the donor might feel reassured at being followed, as perhaps would the transplant surgeons. The UK Guidelines for Living Donor Kidney Transplantation, prepared by a working party of the British Transplantation Society and the Renal Association, do suggest life long follow up of donors as a matter of good practice. This is understandable and very clearly expressed on page 68 of that document. (Level 4) (9)

References

Question 18

Is there a volume/outcome relationship for renal transplantation?
Are there data by renal transplant centre or by transplant surgeon?
If there are no data for renal transplantation, are there data for other procedures?

Comments on the Evidence

The search strategy generated 139 references and seven papers were deemed eligible for inclusion. Six papers, four from the USA (4, 6, 7, 8) and two from Europe (1, 5) were either chapters or original papers studying primarily volume and outcomes in renal transplantation or several forms of transplantation. The other was a CRD report entitled *The relationship between hospital volume and quality of health outcomes*. This report, however, did not include renal transplantation. Overall, five of the six papers showed no link between the volume of transplants carried out in a centre and graft survival. One studied volume of transplants performed per surgeon, and it showed no effect either. An extensive French study (5) published in 1999, studying all 43 renal transplant centres transplanting between 1991 and 1996, showed that there were differences between centres but that this did not reflect the volume of activity undertaken by the transplant team. They included all teams performing a total of more than 15 transplants in the five years between 1991 and 1996. This group did find a correlation between volume and outcome for liver and lung transplantation, but not for heart or kidney transplantation.

One review published by the Swedish Council on Healthcare Technology Assessment in 1992 (1) disagrees, to an extent. They studied all forms of transplants, including renal. They showed that in the USA between 1968 and 1971 centres performing fewer than 25 renal transplants per year had poorer graft outcomes at one year. The authors quote a further paper (2) which reported the results of 71 transplant centres in the USA which carried out more than 20 transplants per year. The article did not apply statistical tests to the volume/outcome relationship and hence is less convincing, but the graph apparently did show a clear relationship. The authors commented, however, that one-year graft survival in the centres ranged from 56% to 100%, but that if they had included all centres where less than 20 transplants were done, the range would have been 0% to 100%. This indicates that centres doing fewer than 20 transplants a year have worse outcomes. They do not state when these transplants were carried out. Their overall conclusion is that the outcome/volume relationship has not been thoroughly studied in the field of kidney transplantation.

Summary statements

- Overall there is no convincing evidence that the volume of renal transplants performed in a centre affects outcome. (Level 2) (5, 6, 9) Studies performed between 15 and 30 years ago showed some effect (2). More recent studies do not confirm this.

- One French study did show differences in graft survival between units but this was not accounted for by differences in size of the units. (Level 2) (5)

References


Question 19

Does prophylaxis against Cytomegalovirus (CMV) infection improve outcomes in renal transplantation?

**Comments on the evidence**

CMV infection can occur after transplantation, particularly if the transplanted organ is positive for CMV and the recipient has shown no evidence of previous exposure.

There is good evidence from a Cochrane systematic review of trials up to 1998 and subsequent RCTs that prophylactic regimens using antiviral agents are effective in reducing the incidence of CMV disease and CMV infection in renal transplant patients. The Cochrane sub-group meta-analysis (1) indicated that both ganciclovir (Relative Risk 0.45, 95% CI 0.34 to 0.59) and high dose aciclovir (RR 0.42, 95% CI 0.24 to 0.73) were effective in reducing the incidence of CMV disease in solid organ transplantation. Subgroup analysis confirmed that the benefit of antiviral treatment occurred in renal transplantation. Lowance et al (5) in a robust RCT of 616 randomised patients demonstrated that prophylaxis with 90 days of oral valaciclovir reduced the incidence of CMV disease at 90 days (CMV seropositive donor to seronegative recipient: placebo 45%; valaciclovir 3%; CMV seropositive or negative donor to seropositive recipient: placebo 6%; valaciclovir 0%) and at six months (CMV seropositive donor to seronegative recipient: placebo 45%; valaciclovir 16%; CMV seropositive or negative donor to seropositive recipient: placebo 6%; valaciclovir 1%). Valaciclovir also appeared to reduce the incidence of acute rejection and other herpes virus infections.

Two RCTs (7 and 2) have indicated that ganciclovir prophylaxis is more effective than aciclovir.

Unfortunately there are no good RCTs comparing 1) intravenous vs oral ganciclovir 2) duration of treatment – most studies have used three to four months of prophylaxis.

An RCT (4) demonstrated no difference in incidence of CMV disease and possible cost-savings with a pre-emptive strategy, although very frequent testing of patients was required up to a year following transplant, and careful scrutiny of the results coming back from the laboratory, so that treatment can begin.

Although it is methodologically unsound to rank the effectiveness of different agents which have been compared to placebo in different trials, ganciclovir and valaciclovir appear to be the most effective.

There are no robust trials comparing these two agents in renal transplantation.

Valaciclovir is not yet licensed for this indication in the UK.

Valganciclovir (which can be given once per day) has recently been shown to be as effective as oral ganciclovir in preventing CMV disease in an RCT in organ transplantation (6). Not yet licensed in UK for this indication.

Passive immunisation was not included in the Cochrane review. Wirnsberger et al (8) found no significant difference in a RCT of 83 patients.

Different immunosuppression regimens, different risk groups (CMV serology) and different organ transplants make comparisons across different trials problematic.

**Summary statements**

- CMV disease is a cause of morbidity, mortality and hospitalisation in renal transplant recipients.
- Antiviral treatment is effective in preventing CMV disease. (Level 1) (1, 5, 7, 2, 6)
- Oral valaciclovir, ganciclovir and valganciclovir have all been shown to be effective. (Level 1) (1, 5, 7, 2, 6)
- At present ganciclovir is the only drug licensed for this indication.
There is some RCT evidence to suggest pre-emptive treatment can be used instead of routine prophylaxis, but given the frequency of patient testing it may be difficult to achieve the same results in routine clinical practice as compared with a trial. (Level 1) (4).

References

Question 20

Does prophylaxis against Pneumocystis Carinii (PCP) infection improve outcomes in renal transplantation?

Comments on the evidence

PCP is a relatively rare infection that occurs in immunosuppressed patients.

A single RCT (1) of 132 randomised patients found no significant difference in the incidence of PCP between treatment group (co-trimoxazole) (0/66) and placebo (1/66). Estimated incidence of PCP in untreated patients with similar immunosuppression protocols is approximately 10% (4). The low incidence in the placebo group may have made it difficult to demonstrate a beneficial effect. A further RCT (2) of 103 randomised patients found a significantly lower incidence of PCP with co-trimoxazole (0/52) compared with ciprofloxacin (7/51) prophylaxis.

The randomised evidence to support co-trimoxazole prophylaxis is limited and is largely from the USA, where the routine use of more potent immunosuppression is likely to be associated with a greater incidence of PCP. However PCP has significant morbidity and mortality; retrospective studies in renal transplantation and prospective studies in the HIV population have indicated a substantial reduction in PCP with co-trimoxazole and it has an acceptable adverse event profile in the renal transplant population. Its routine use as prophylaxis should be recommended. There is no clear data to support dose or duration of treatment recommendations, though most patients in the randomised trials completed at least six months of prophylaxis.

In addition co-trimoxazole significantly reduces the incidence of urinary tract infections and other bacterial infections (1) both during initial hospitalisation and at out-patient follow up. Ciprofloxacin was shown to be even more effective in the reduction of urinary tract infections (2).

Summary statements

- PCP is a life-threatening though relatively rare complication of immunosuppression following renal transplantation.
- Co-trimoxazole is an effective and safe prophylactic agent against PCP. (Level 1) (1, 2)
- In addition it reduces the frequency of post-transplant urinary tract infections. (Level 1) (1)
- There is no clear evidence to recommend a specific dose or duration of treatment.
- Dapsone and nebulised pentamidine are alternatives for patients intolerant of co-trimoxazole. (3, 5, 6)

References

Question 21

How does graft outcome vary with warm and/or cold ischaemia time?

Comments on the evidence

The search strategy generated 735 references after duplicate references found by more than one database were removed. A total of 33 papers were ordered for further appraisal out of which six were excluded as they did not address the issue in question. 23 studies concerned exclusively Cold Ischaemia Times (CIT) and two exclusively Warm Ischaemia Times (WIT) (19, 12). Two papers had dealt with both CIT and WIT (10, 18).

Cold ischaemia times

There were seven studies that had used 24 hours as their cut-off point for high and low CITs (1, 6, 16, 21, 23, 24, 27). One study analysed the effects of both age of donor and CIT (the cut-off for age was 55 years and that for CIT was 24 hours) (17). This study showed that CIT > 24 hours increased Delayed Graft Function (DGF) by 10% among similar age groups. Long-term graft function however was not affected. One study showed the risk of thrombosis in paediatric transplants when CIT was greater than 24 hours (5.6% vs 3.2%) (24). One study showed that preserving kidneys in HTK (Histidine-Trytophan-Ketoglutarate) was associated with a significant increase in the incidence of DGF when CIT was > 24 hours, when compared with preserving kidneys in UW (University of Wisconsin) solution (50% vs 23.9%) (21). An analysis of 458 cadaveric transplants data showed that the relative risk for graft failure with a CIT of > 24 hours vs < 24 hours was 1.9 (27).

Several other studies have chosen other cut-off points for CIT. One study found that DGF was lower with mean CIT of 22 hours (Group1) as opposed to 28.1 hours (Group2) (15). This study also found that 1-year graft survival was 93% in Group1 vs 90% in Group2. One study (16) analysing data from the UNOS (United Network for Organ Sharing) Transplant Registry showed that a CIT of > 36 hours negated the benefits of a 0 HLA mismatched transplant. The five-year graft survival in 0 mismatch kidneys with CIT <36 hours was 75% compared with 71% in patients with 0 mismatches and >36 hours CIT (16). A study of 1157 transplants by Groenewoud showed that the relative risk for DGF was 1.84 when CIT was 25-36 hours compared with CIT of >36 hours (11). One analysis of data from the UNOS registry showed that the risk of DGF increased from 17% when the CIT was <12 hours to 39% when it was between 49 and 72 hours (7), and another analysis showed that CIT of >35 hours had a very modest effect in reducing the one year and five-year graft survival rates (8). One study from Manchester, UK showed decreased one-year and five-year graft survival rates with CIT of > 26 hours (9). A study of routine transplant biopsies in children showed an association between Chronic Allograft Nephropathy and CIT of 31±13 hours compared with 25±14 hours for other findings on biopsy (3). One study has surprisingly shown that whilst prolonged CIT increased the incidence of DGF it had no effect on one-year graft survival (20). One study showed that both DGF and hospital stay were reduced significantly with shorter CITs (19±3.7 hours vs 23±4.1 hours) (22).

Some studies have shown decreased graft survival and increased risk of DGF with cold ischaemia times less than 24 hours. These times are variously, 18 hours, 20 hrs and 22 hrs (15, 26, 2, 4, 10). One study showed that CIT was more important in cadaveric donors of more than 50 years of age than in kidneys from younger donors (4). A study of effect of CIT on early graft function showed that incidence of Acute Tubular Necrosis was increased in the group with CIT of 19.2±6.9 hours when compared with a group with CIT of 14.1±5.7 hours (25).

Four studies that assessed the relationship between CIT and rejection did not find a significant relationship (27, 25, 6, 18).

Several studies have looked at the interaction between CIT and age of donor (17, 7, 8, 9, 2, 4) and between CIT and HLA matching (16, 9, 2, 6, 5, 13). One study showed that the graft survival benefit of donor aged < 50 years was lost with CIT > 26 hours (9). Two studies showed that prolonged CIT predominantly affected kidneys from donors aged > 60 years (7, 4) and one study showed it to affect mainly survival of donor kidneys aged < 10years (8).
One study showed that prolonged CIT (> 14 hours) increased the production of HLA Class I antibodies (5). Two studies showed that the benefit of HLA matching was lost with prolonged CIT (16, 9). In one study the beneficial impact of HLA matching seems to be less than the detrimental effect of CIT in the first year but its relative importance increases with time (2). A study by Cantarovich et al of 130 cadaveric transplants divided patients into four groups based on the number of HLA mismatches and CIT cut-off at 24 hours (6). There was no difference between the four groups as far as graft and patient survival was concerned. The data suggested HLA matching, but not CIT, was important in reducing acute rejection. Iwaki et al showed that matching of Class II HLA antigens had a neutralising effect on CIT (13). The two match HLA-DR recipients had the same graft survival regardless of CIT, but 0 match HLA-DR kidney recipients had worse graft survival with increased CIT (>40hours).

Warm Ischaemia Times (WIT)

Only four papers dealt with WIT (10, 18, 12, 19). One study showed that patient subsets with WIT of 15-29 minutes and > 30 minutes had lesser five-year graft survival when compared with transplants with WIT of ≤ 14 minutes (12). One study from Leicester, UK showed that two transplants from Non-Heart Beating donors both failed when the WIT exceeded 40 minutes (18). The average WIT in that study was 25 minutes. One study looked at WIT in living donor transplants and concluded that the range of WIT achieved in their transplant unit (1-9 minutes) did not affect the survival of the grafts (19). They have however mentioned that patients with longer WIT in their study demonstrated better survival to first episode of rejection. One study comparing transplants from Non Heart Beating Donors to Heart Beating Donors concluded that the best cut-off point for WIT was 45 minutes and that for CIT was 22 hours (10). They had shown that patients with both long WIT (> 45 minutes) and CIT (> 22hours) had a relative risk of 6.8 for graft loss when compared with both short WIT and CIT. The relative risk for graft loss was 2.8 when patients with short WIT/long CIT were compared with patients with short WIT/short CIT.

Summary statements

- The evidence suggests that prolonged WIT and CIT lead to increased risk of DGF and, in some studies, to increased graft loss. It is however difficult to ascertain a cut-off point for both the ischaemia times given the wide ranges reported. It is also clear that both the age of the donor kidney and the HLA matching have an equally important role in graft survival. One has therefore to strike a balance between achieving HLA match and keeping the ischaemia times as short as possible. Warm Ischaemia Times should not exceed 30 minutes. (Level 2) (12, 18, 9)
- Cold Ischaemia Times should be less than 24-27 hours. (Level 2) (1, 6, 16, 21, 23, 24, 27)

References:

Included Papers


Excluded papers


Question 22

At what point should transplant recipients be released by the transplant centre to the care of the local nephrologists?

Comments on the evidence

Only two papers were retrieved; one concerned liver and the other renal transplantation, both from the USA. The one which concerned renal transplantation concerned returning the patient to ‘community nephrologists’. The situation is rather different in the UK, with all nephrologists being trained in transplantation. The authors suggested that the transplant centre follow the patients for four to six weeks before returning/releasing to the community nephrologist; but that this would vary in accordance with the degree of involvement the particular nephrologist had with the transplant centre, his/her experience and the patient's condition, for example whether they had undergone acute rejection episodes.

Summary statements

- No specific comment can be made from the literature on this point as regards the UK.
- The suggestions made in the last sentence above are however sensible.

References

Included study


Excluded study

2. McCashland TM. Post transplantation care: Role of the primary care physician versus the transplant centre. Liver Transplantation 2001; 7: S2-12
RESEARCH IN PROGRESS OR RECENTLY COMPLETED,
FUNDED BY THE DEPARTMENT OF HEALTH

Health Technology Assessment Programme (HTA)

3. Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: a review; by A MacLeod, A Grant, C Donaldson, I Khan, M Campbell, C Daly, et al. (HTA ref: 93/40/02 – published 1998, Vol 2, No 5)

4. A policy for the drug treatment of high blood pressure; M Law, N Wald, J Morris. (HTA ref: 93/05/01 – published 2003, Vol 7, No 31)

5. An evaluation of the cost-effectiveness and quality of care of renal replacement therapy provision in satellite units; Dr P Roderick. (HTA ref: 95/31/05)

6. Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus (CMV) disease in immunocompromised individuals; Dr D Westmoreland. (HTA ref: 96/09/14)

7. Systematic review of urine albumin testing for early detection of diabetic complications; Dr D Newman. (HTA ref: 96/33/02)


9. Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure; G Mowatt, L Vale, J Perez, L Wyness, C Fraser, A MacLeod et al. (HTA ref: 01/46/01 – published 2003, Vol 7, No 2)

10. The clinical effectiveness and cost effectiveness of immuno-suppressive regimens for renal transplantation; Dr R Taylor. (HTA ref: 01/59/01)

11. A systematic review of tests for the diagnosis and evaluation of urinary tract infection in children under five years; Prof J Kleijnen. (HTA ref: 01/66/01)

Following identification of priority areas by the HTA Prioritisation Strategy Group, the National Coordinating Centre for Health Technology Assessment, on behalf of the NHS Director of Research and Development, is to commission research on proposals including the following:

12. Effect of Staphylococcus aureus on peritoneal catheter-related infections. (ref: 03/42)

For further information, please see the Health Technology Assessment Programme website at: www.ncchta.org

Department of Health Policy Research Programme

13. Prof T Feest, The UK Renal Registry, with support from Dr P J Roderick. UK Renal Specialty Survey. Published as Chapter 3 of the Third Annual Report of the UK Renal Registry, Bristol, December 2000 (www.renalreg.com)


15. Prof T Feest, The UK Renal Registry, with support from Dr P J Roderick. UK Renal Specialty Survey 2002.
AREAS FOR FURTHER RESEARCH

In compiling this report the Evidential team identified topics where further research would be helpful. In general, there is a need for more randomised controlled trials in the field of Renal Replacement Therapy (RRT) with accompanying economic analyses. Cohort studies give valuable information but many are small with short term follow up. There is also a need for rigorous research into aspects of the process of patient care including dietary, social work, patient information and counselling.

Research Questions

1. What types of education and information given to patients before and during their time on RRT are both effective and cost-effective?

2. Which forms of advice, support and counselling for patients approaching and undergoing RRT are effective and cost effective?

3. Which dietary interventions for patients approaching and undergoing RRT are effective and cost-effective?

4. Which of the available dialysis modalities is most effective and cost-effective, and to what extent does this vary with the needs of the individual patient? Specifically, what is the effectiveness and cost-effectiveness of haemodialysis and haemodiafiltration in patients undergoing dialysis for established/end stage renal failure (ERF)?

5. What criteria should be used to select patients for transplantation and what criteria are currently used?

6. How many patients have their first dialysis using permanent forms of vascular access (ie some form of fistula or graft not a ‘permanent’ form of catheter) and what are the barriers to obtaining such access?

7. How many prevalent patients at a given time point have permanent vascular access?

8. What proportion of patients present within 3 and 6 months of their first dialysis?

9. Is radiological monitoring of grafts and fistulae effective and cost-effective?

10. What are the effectiveness and cost-effectiveness of various frequencies and durations of dialysis sessions?

11. What is the optimal target for haemoglobin for patients on dialysis, and does this vary for different patient groups?

12. To what extent are patients with ERF treated in appropriate environments when they are in-patients?

13. What is the optimum environment for dialysis for patients with ERF, taking into account distance from a unit and transport arrangements?

14. Do patients think their transport arrangements for haemodialysis are adequate?

15. Does APD offer advantages over CAPD for all (or some) patients appropriate for PD? (Such a study should include a patient preference questionnaire).

16. What is the effectiveness and cost-effectiveness of models of provision of renal transplant services in the UK and other European countries?