THE EVIDENCE BASE

for the
National Service Framework
for Renal Services

Part Two:
Chronic Kidney Disease,
Acute Renal Failure and
End of Life Care

Gateway reference: 5965

CONTENTS

Acute Renal Failure

INTRODUCTION

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

How the Review of Evidence was Undertaken

This report is the result of reviewing the evidence for Part Two of the National Service Framework (NSF) for Renal Services. These modules cover chronic kidney disease (CKD), acute renal failure (ARF) and end of life care. 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 (where relevant) excluded studies. Summary statements were given a level of evidence as described in the table below. The reports were then sent to the Department of Health to aid the development of the National Service Framework.

Levels of Evidence

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

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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Note

This paper is subject to peer review.

CHRONIC KIDNEY DISEASE

Question 1

How important or effective is the control of hypertension in preventing decline in renal function - at any level of glomerular filtration rate (GFR)? Does renal function decline if essential hypertension is untreated? In patients with recognised renal impairment, does hypertension arrest or slow the decline in renal function?

Comments on the evidence

Hypertension and Chronic Kidney Disease (CKD)

First of all, the issue of whether hypertension causes CKD was explored. The K-DOQI guidelines clearly state that in CKD patients, hypertension is associated with more severe decline in renal function and is an important cardiovascular risk factor (10). The main focus of this question was the effect of controlling blood pressure in hypertensive patients, both with normal and abnormal kidney function. The scope has, however, been broadened to evaluate the role of antihypertensives in the whole CKD population, ie even in normotensive CKD patients. Given the high prevalence of hypertension in diabetic patients, and the high cardiovascular morbidity associated with diabetic nephropathy, the role of antihypertensives in this patient group has also been explored.

Two studies were excluded as they did not include progression of renal insufficiency as an outcome measure (29, 31) and one was a duplicate paper (30).

A. If essential hypertension is left untreated does renal function decline (assuming normal renal function from the start)?

One meta-analysis of ten randomised controlled trials (RCTs) with a total of 25,521 'non-malignant' hypertensive patients did not show any reduction in risk of developing renal dysfunction between treated and untreated patient groups (7). In 'non-malignant' hypertension, the blood pressure usually remains below 200/120 mm Hg and there is no damage to any of the organs as a result of hypertension, ie there are no retinal haemorrhages or exudates in the eye and no fibrinoid necrosis of the arterioles in the kidney on pathological examination. In this systematic review, the follow-up periods of the studies ranged from 1.4 years to 7 years. The definition of renal dysfunction varied between different studies, with one study defining it as blood urea nitrogen of more than 7mmol/l to one defining it as death from renal disease. Renal dysfunction as defined by the studies assessed occurred in only 72 of the total 25,521 patients. This systematic review shows how few people get renal damage as a result of 'non-malignant' hypertension in the follow-up periods described. The follow-up periods in the included trials may, however, be too short for the development of renal dysfunction. Also, ten RCTs may not be the most appropriate type of study to assess the development of renal failure in a given population.

B. Studies in hypertensive patients both with and without CKD

In the Hypertension Optimal Treatment (HOT) trial (23), with 18,597 patients and follow-up duration of 3.3 to 4.9 years, there was no change in baseline and final serum creatinine concentrations for all the diastolic blood pressure target groups ($\leq$90 mm Hg, $\leq$85 mm Hg, $\leq$80 mm Hg). The results of the study have to be interpreted with caution, as this study was not designed to measure the effect of blood pressure lowering on renal function.

In the United Kingdom Prospective Diabetes Study (25), with 1,148 hypertensive Type 2 diabetic patients with a median follow-up duration of 8.4 years, those achieving a tighter blood pressure control (144/82 mm Hg), when compared to those achieving less tight control (154/87 mm Hg), had a 295 reduction risk of urine albumin concentration of ≥50 mg/l, and a 39% non-significant reduction in risk for proteinuria of ≥300 mg/l. This study did not measure effect of blood pressure control on GFR.

One study (16) of blood pressure in patients with mild to moderate hypertension (mean serum creatinine 113µmol/l) showed that patients with diastolic blood pressure ≤ 95 mm Hg and those with diastolic blood pressure ≥95 mm Hg did not differ in the slope of reciprocal creatinine concentrations plotted for the study duration (5 years). It has to be noted that the diastolic blood pressure cut-off chosen in this study is far higher than those recommended by various hypertension management guidelines.

C. Studies in CKD patients with hypertension

In the Modification of Diet in Renal Disease (MDRD) study (21), 840 patients with a lower achieved blood pressure (mean arterial pressure (MAP) ≤92 mm Hg for those ≤60 years of age and ≤98 mm Hg for those ≥61 years of age) had significantly reduced proteinuria and decline in GFR, compared with those with higher achieved blood pressure (MAP ≤107 mm Hg for those ≤60 years of age and ≤113 mm Hg for those ≥61 years of age). The mean duration of follow-up for this study was 2.2 years.

In the African American Study of Kidney Disease and Hypertension (AASK) trial (27), 1,094 adult African Americans with renal failure (creatinine clearance 20 to 65 mls/min) were randomised to either 'usual' (MAP 102 to 107 mm Hg) or 'lower' (MAP ≤92 mm Hg) blood pressure groups. Patients in the lower target blood pressure group (average achieved blood pressure 128/78) did not have any difference in the risk of the clinical composite outcome of reduction of GFR by more than 50%, compared with those in the higher group (average achieved blood pressure 141/85 mm Hg). The follow-up duration in this study ranged from 3 to 6.4 years

D. Studies in CKD patients both with and without hypertension

Several trials of antihypertensive agents have been conducted in patients with CKD, who were included regardless of whether they had hypertension or not. Evidence has only been included from meta-analyses of these trials (5, 6, 8, 9, 12, 28). Two meta-analyses included trials with both diabetic and non-diabetic CKD patients (5, 8), two included trials with non-diabetic CKD patients only (6, 12) and two had trials exclusively on diabetic CKD patients (9, 28).

Reduction in blood pressure per se may slow decline in renal function (9, 8). Kasiske et al (8) included 100 studies in their meta-analysis of trials in diabetic nephropathy, and concluded that blood pressure reduction in itself resulted in benefit in GFR preservation of 3.7 ± 0.92 ml/min for each 10mmHg reduction in mean arterial pressure (MAP). One meta-analysis of 11 RCTs of Angiotensin Converting Enzyme (ACE) inhibitors (8) in 1,860 patients with CKD has reported, that kidney function is least likely to decline in the systolic blood pressure range of 110 to 129 mm Hg.

According to one retrospective study (3) which derived data from patients newly commenced on chronic dialysis, a diastolic blood pressure of less than 90 mm Hg, was associated with significantly lesser rate of decline of renal function, than a diastolic blood pressure of more than 90 mm Hg. This study had a follow-up period of 7 to 111 months.

E. Role of Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) in preventing renal function decline in CKD patients

ACE inhibitors have been shown to improve renal function in patients with CKD, both in terms of reducing rate of decline of GFR and decreasing proteinuria (5, 6, 8, 12). This effect is seen both in diabetic and non-diabetic CKD patients (8, 12). The improvement in renal function is over and above that which can be attributed to the effect of ACE inhibitors on reducing the blood pressure per se (5, 8, 12). Whilst ARBS have been shown to be efficacious in diabetic nephropathy, evidence on the efficacy of ARBs in the setting of non-diabetic CKD is awaited. In the CO-OPERATE study, the combination of ACE inhibitors and ARB was more effective than ARB or ACE inhibitor alone in protecting renal survival in non-diabetic CKD patients (18).

F. Diabetic Nephropathy

A number of prospective studies show a strong relationship between a higher level of blood pressure and an increased risk of kidney failure and worsening kidney function in diabetic kidney disease (1, 20, 11). Two meta-analyses support the reduction of blood pressure for the improvement of renal function in CKD due to diabetes (9, 28). There is strong evidence to show that ACE inhibitors are superior to other agents in slowing decline in kidney function in nephropathy due to Type 1 diabetes (13), and ARBs over other antihypertensives are superior in the setting of Type 2 diabetes (2, 14). ACE inhibitors have been shown to be superior to other antihypertensives (Chlorthalidone) in a large subgroup of patients with diabetic nephropathy (GFR less than 60 mls/min) in the ALLHAT study (22), with respect to decline in renal function. ARBs have not yet been assessed with long-term controlled trials in Type 1 diabetic patients. A recent systematic review (24) has concluded that both ACE inhibitors and ARBS are similar in their efficacy with regard to renal outcomes in diabetic nephropathy. However, whilst ACE inhibitors reduce all cause of mortality in these patients, the ARBs have not been shown to have a beneficial effect on mortality.

What the published guidelines say:

The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (4) advises achievement of a blood pressure of less than 130/85 mm Hg in patients with CKD (GFR less than 60 mls/min or albuminuria more than 300 mg/d). The American Society of Hypertension also advises a target blood pressure of less than 130/85 mm Hg in patients with renal parenchymal disease (15).

The 2001 Canadian recommendations for the management of hypertension are that for patients with non-diabetic renal disease, the target blood pressure should be less than 130/80 mm Hg, and for those with proteinuria more than 1 gm/d, the target blood pressure should be less than 125/75 mm Hg (17).

The British Hypertension Society recommends a target blood pressure of less than 130/80 mm Hg for patients with CKD and less than 125/75 mm Hg for those with proteinuria more than 1 gm/day (26).

Summary statements

- The only systematic review looking at renal effects of antihypertensive treatment for blood pressure control in the hypertensive population did not show any reduction in risk for developing renal dysfunction in the study group on active treatment, and this may be due to the low incidence of renal failure in the general population. (Level 1) (7)
- There is some evidence to support reduction in blood pressure for slowing the decline in renal function in hypertensive patients with CKD. (Level 1) (21)
- Blood pressure reduction has been found to have a beneficial effect on renal function in CKD patients both with and without hypertension. (Level 1) (9, 8)

- ACE inhibitors have been proven to be superior to other antihypertensives in reducing decline in renal dysfunction in patients with kidney disease, and their renoprotective effect is independent of their antihypertensive properties. (Level 1) (12, 8)
- There is strong evidence to show that ACE inhibitors are superior to other antihypertensives in slowing decline of renal function in patients with CKD due to Type 1 diabetes (13), and ARBs are superior to other antihypertensive agents in Type 2 diabetes patients. (Level 1) (2, 14)

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Questions 2 and 3

Question 2

How important or effective is primary prevention of cardiovascular disease by reducing cardiovascular risk (lipids, smoking, weight, diet [healthy diet not low protein] and possibly exercise) in preventing or slowing decline in renal function?

- Does stopping smoking arrest or slow the decline in renal function in patients with some degree of renal impairment?
- In obese patients with some degree of renal impairment, does losing weight arrest or slow the decline in renal function?
- Does participating in exercise programmes slow the decline in renal function in patients with some degree of renal impairment?

Question 3

How important/effective is secondary prevention of cardiovascular disease in those with existing cardiovascular disease by reducing cardiovascular risk (lipids, smoking, weight, diet [healthy diet not low protein] and possibly exercise) in preventing or slowing decline in renal function?

- Does stopping smoking arrest or slow the decline in renal function in patients with some degree of renal impairment?
- In obese patients with some degree of renal impairment, does losing weight arrest or slow the decline in renal function?
- Does participating in exercise programmes slow the decline in renal function in patients with some degree of renal impairment?

Comments on the evidence

These two questions were addressed together as no studies, with the exception of the ASCOT study (9), mentioned the presence or absence of cardiovascular disease in their study populations.

Three studies were excluded as they did not address the topic in question (11, 12, 13). One paper (Department of Veterans Affairs Medical Research Service 2003), which is an ongoing trial, was excluded as the intervention is not one among the ones in consideration for this question.

Four were from Europe (4, 6, 7, 8), two from the USA (3, 5) and one was a joint Anglo-Swedish study (9).

Of the included studies, six were from Europe (1, 2, 4, 6, 7, 8), one was from Canada (10), two from the USA (3, 5) and one was a joint Anglo-Swedish study (9).

Smoking

One case-control study (8) in patients with CKD due to primary nephropathies (glomerulonephropathies or tubulointerstitial nephritis) showed that current smokers had a significantly faster decline in creatinine clearance over a 24-month follow-up period. 23% of current smokers as opposed to 6% of ex-smokers had to be commenced on renal replacement therapy (RRT).

Exercise

One RCT study (4) with 30 CKD patients and a median follow-up period of 20 months failed to show any difference in the decline of renal function, assessed by GFR, between patients allotted to exercise training and those to no intervention. However another (3) showed that GFR showed a slight but significant improvement (24.76 to 26.35 mls/min) in patients on both a low-protein diet and resistance exercise training compared to patients on low-protein diet alone. This study had only 18 patients for the outcome assessed with a very short follow-up period of 12 weeks. Low-intensity aquatic exercises were shown to result in small (n=20) and statistically insignificant increases in GFR (60.0 $\pm$7.4 to 67.3$\pm$10.1 mls/min) in a 12-week case-controlled study (7).

Obesity

In a randomised study of obese patients (6), those who achieved weight loss using a low-calorie normoproteinic diet showed stable creatinine clearance, whereas patients in the control group had significant deterioration in their creatinine clearance. It should however be noted that creatinine clearance did not show significant correlation with weight loss.

Lipids

Post hoc analysis of several large-scale trials (1, 10) of statins in dyslipidaemic patients both with normal and impaired renal function has shown that statins slow renal function decline in concert with antihypertensive and antiproteinuric measures such as ACE inhibitors. In the ASCOT trial (9) (n=10,305), which was a primary prevention RCT with atorvastatin in patients with normal or low cholesterol levels, there was no significant difference between treatment and placebo group patients in the risk for development of renal failure. The ASCOT study included patients with microalbuminuria/proteinuria, but excluded patients with creatinine values of more than 200 μmol/l. In one prospective controlled study (2) (56 patients, follow-up 1 year), atorvastatin was compared with placebo in patients with CKD (mean creatinine clearance -50.4 ml/min) and hypercholesterolaemia. This study found that atorvastatin reduced proteinuria significantly (p less than 0.01) when compared to placebo. The creatinine clearance of patients on atorvastatin was found to be stable at the end of study period, whilst that of patients on placebo had declined significantly.

One meta-analysis (5) has reported that the use of lipid reducing agents in patients with renal diseases results in lower rate of decline in GFR (0.156 ml/min/month, 95% CI 0.026 to 0.285 ml/min/month). The trials included were very small, and the total number of patients included in the analysis was only 384. The patient groups, interventions used and the follow-up periods in the trials assessed were too varied to be combined meaningfully. The authors have also not searched major medical databases such as EMBASE and Cochrane Registry of Controlled Trials, thereby missing trials that were not listed in the MEDLINE database. Meta-analysis was done using the 'fixed effects' model, which is not as robust as the 'random effects model', which assumes variations in treatment effects between the studies. The inclusion of non-randomised studies in the meta-analysis lessens the validity of the results. Considering the methodological drawbacks of this review, the results should be interpreted with caution.

Most of the studies suffered from small population groups (range: 20 to 90 patients) and very short study periods (range: 12 weeks to 24 months). The studies were neither powered adequately nor were of sufficient duration to detect differences in the long-term renal function outcomes.

Summary statements

- There is weak evidence to support cessation of smoking, obesity and use of resistance exercises to prevent/slow decline of renal function in patients with CKD. (Level 3) (3, 6, 8)

- Although there is currently some evidence (Level 1) to support use of statins in the prevention/slowing of decline of renal function in patients with mild renal impairment (2), further long-term, large scale RCTs are needed, especially in patients with moderate to severe renal failure.

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Question 4

How important/effective is reducing bladder outflow obstruction in preventing CKD (especially drug treatment for benign prostatic hypertrophy)? ie is there any evidence that when treated for benign prostatic hypertrophy either using drugs or by resection, that any decline in renal function is arrested or slowed?

Comments on the evidence

Two papers were excluded, as they were duplicate papers (11, 12) and one because of poor reporting of results (13).

Four of the included papers were from the UK (1, 2, 4, 9), two from the USA (3, 7), one from Finland (5), one from Israel (6) and one from Japan (10). It was not possible to determine the country of origin of one paper (8) as it was identified from the review article by Klahr (3).

In one study of 21 patients (10) with acute urinary retention and severe renal failure (mean serum creatinine 11.8 mg/dl), 81% were reported to have recovered renal function with creatinine levels of $\leq$ 2mg/dl.

One study (9) assessed outcomes in 19 patients presenting with late severe renal failure (mean serum creatinine 1158 µmol/l) due to prostatic outflow obstruction. In this study, 48% of survivors required long-term dialysis, and the remaining 52% only had partial renal function recovery.

In the study by McClelland et al (4), of 67 patients with ARF due to obstructive uropathy, which had a median follow-up of 58 months, admission levels of renal function parameters were not given, but 19% were reported to have had complete renal function recovery.

In one study (2) of 32 patients with 'high pressure chronic retention of urine', who underwent bladder outflow surgery, the admission mean creatinine clearance was 53 mls/min (range: 9 to 122 mls/min). 84% of the patients in this study had improvement or stabilisation of renal function (post-obstruction relief mean creatinine clearance 81.9 mls/min, range: 38 to 164 mls/min). Another study (1) of 21 patients with high pressure chronic retention of urine reported that GFR, creatinine clearance and plasma creatinine levels improved significantly when compared with admission levels following relief of bladder flow obstruction. Mean creatinine clearance during obstruction was 32.5 mls/min, and this improved to 57.3 mls/min three months after relief of obstruction.

Nissenkorn et al (6) reported data from 26 patients who had prostatectomy with pre-procedure residual urine of over 1000 mls. Serum creatinine levels were high in all of the patients. After prostatectomy, 50% of patients had return of serum creatinine to normal levels.

In one study of 25 male patients (5) with acute urinary retention, only 28% of the study population had an elevated serum creatinine and the median serum creatinine at the time of admission was only 100µmol/l (range 75 to 595 µmol/l). 88% of patients were found to have normal serum creatinine levels 6 months after relief of urinary obstruction. The high percentage of patients recovering renal function in this study is not surprising, considering the low proportion of patients with renal failure and the fairly mild degree of renal impairment on admission.

The review by Klahr et al (3) mentions a study (8) in which 12 patients were followed up 10 to 90 days after prostatectomy for bladder outflow obstruction. The GFR showed an improvement in 50%, deterioration in 42% and stable levels in 8%.

Novakovic et al (7) showed that patients who had elevated levels of both serum creatinine and β_2 microglobulin were less likely to recover renal function after the obstruction was relieved than patients

who had elevated serum creatinine alone. This study suggests that serum β_2 microglobulin level may be a predictor of renal recovery in patients with obstructive uropathy.

No studies were found assessing the effect on long-term kidney function of drugs used to relieve bladder outflow obstruction due to benign prostatic hypertrophy.

Summary statements

- Bladder outflow obstruction is associated with a variable but definite risk of CKD. (Level 3) (2, 4, 5, 6, 10)
- The proportion of patients who recover renal function following relief of bladder outflow obstruction varies widely ranging from 19% (4) to 88% (5). (Level 3)
- Studies are needed to assess the effect on long-term kidney function of drugs to treat benign prostatic hypertrophy.

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Question 5

Is there evidence to support the screening of family members of those with CKD or established renal failure (ERF)? It is known that having a family member who has ERF is a risk factor for developing CKD. Is there any evidence that screening the general population or the family members of those with ERF is worthwhile?

Comments on the evidence

Eight papers were excluded as they were duplicate publications (25, 26, 27, 30, 31, 32, 33, 35), one was a review article with the description of an ongoing screening study with no relevant results (28), and four studies did not address the topic in question (29, 34, 36, 37).

Studies in the general population

The NHANES III survey, a national cross-sectional study (5) of 13,251 non-diabetic black and white people in the US, showed that 58% of the study population had GFRs of less than 80 mls/min and 0.26% were found to have GFR of less than 30 mls/min. In this study the GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula. Another paper (8), based on the NHANES III study but including diabetic patients also, reported that one in 25 patients with microalbuminuria had a GFR of less than 30 mls/min, and in order to identify one patient with microalbuminuria, one would need to screen three patients with diabetes, seven non-diabetic hypertensive patients or six patients over the age of 60. In this survey it was found that one in three patients with a GFR of less than 30 ml/s min had non micro- or macro-albuminurian and therefore it was evident that screening separately for such albuminuria and renal insufficiency identified different segments of the population.

The Okinawa mass-screening programme is by far the largest population screening study. This screening programme covered all adults aged over 18. In this programme, once each year the doctors, nurses and staff of the Okinawa General Health Maintenance Association visited both occupational and residential sites and screened adults. Whilst all patients had urinalysis, blood tests were done only if abnormal urinalysis, hypertension or any other problems were found, or if participants requested it themselves. Also, since the blood tests were not paid for by the public sector, they were not mandatory, and only those willing to pay for them had the blood tests. The ERF population was defined as patients accepted for RRT.

The total population of Okinawa was 1.2 million. The number of screened adults in 1983 was 107,192, which was approximately 13.7% of all the adult population in Okinawa at that time. In 1994, current dialysis patients who had participated in the original screening were identified through the Okinawa dialysis registry. Only patients who had creatinine levels available at the time of screening in 1983 were analysed.

Out of the original 107,192 participants, creatinine levels in 1983 were available for 14,609. 193 out of the 107,192 participants went on to develop ERF requiring RRT in 1994, with a cumulative incidence of 180 per million population (pmp) per year. Out of the 14,609 patients who had creatinine levels measured in 1983, 811 were found to have elevated creatinine values (more than 1.2mg/dl for men, more than 1.0 mg/d for women), and among that group of patients with elevated creatinine values, 60 went on to develop ERF, with a cumulative incidence of ERF of 440 per million per year in 1994. (see Fig 1).

The results of this analysis reported in the paper by Iseki et al (11) found that proteinuria and haematuria, identified by single dipstick testing of the urine, was associated with significantly higher odds of developing ERF. For proteinuria the adjusted odds ratio was 14.9 (95% CI 10.9 to 20.2) and for haematuria the adjusted odds ratio was 2.3 (95% CI 1.62 to 3.28). Another paper (12), based on a subgroup of the same population as the Iseki (11) study, showed that elevated serum creatinine values

(more than 1.2mg/dl for men, more than 1.0 mg/d for women) were associated with higher odds ratio (men - 5.39, 95% CI 3.39 to 8.32, women- 3.92, 95% CI 2.88 to 5.34) of developing ERF. Similar results were reported in later versions of the Okinawa screening programme (13, 14).

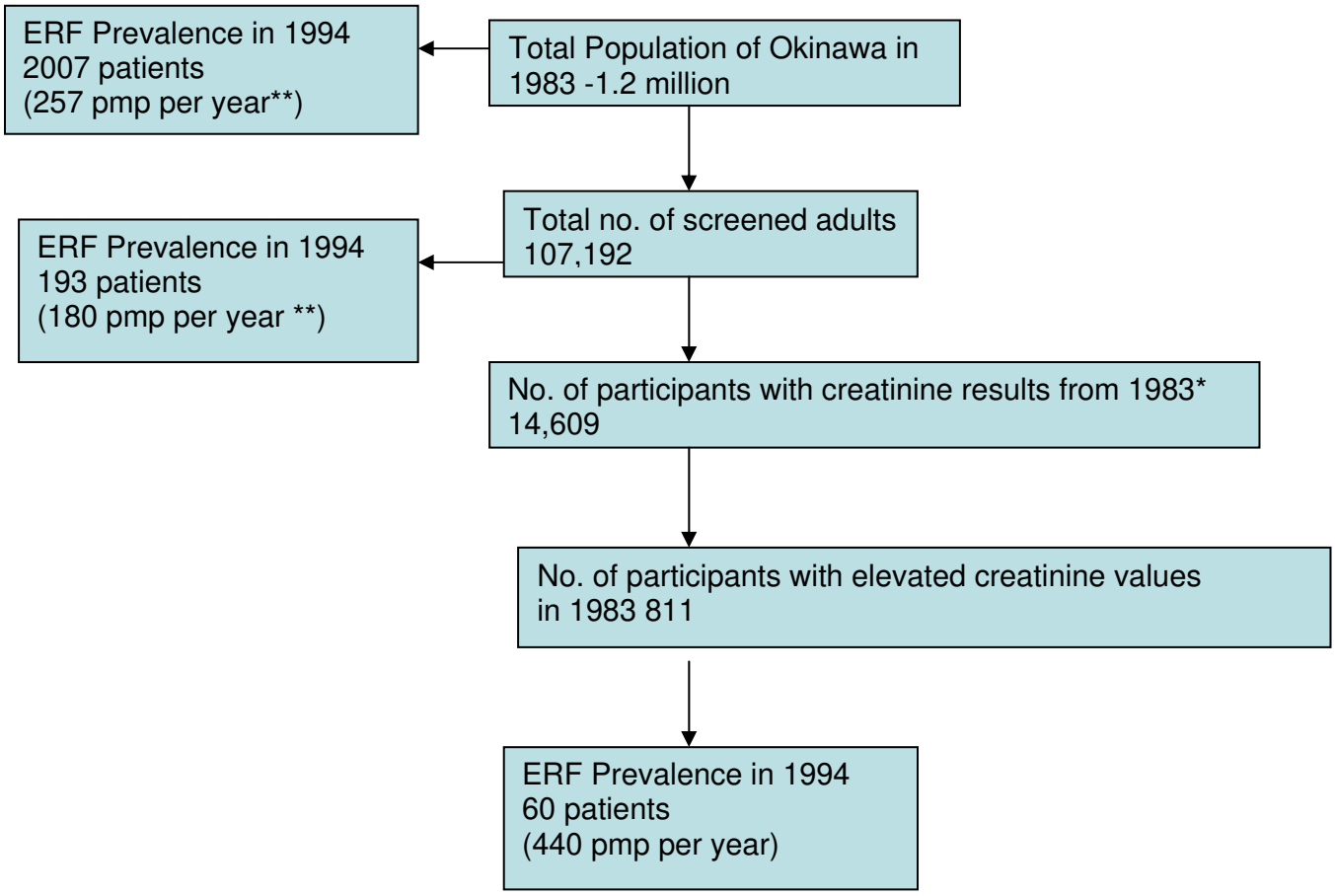

Fig-1 Okinawa mass-screening programme data

* Creatinine was measured only if patients had abnormal urinalysis, hypertension, or other problems, or if participants requested it

** Estimated incidence per year

In the study by Yamagata et al (23) results based on urine dipstick testing of 56,269 adults working in a factory in Japan, between 1983 and 1992, were reported. The mean follow-up period was 5.80±4.42 years. 805 individuals were found to have asymptomatic haematuria and/or proteinuria. None of the participants with persistent haematuria alone developed renal insufficiency. 14.9% of those with both haematuria and proteinuria (n=150) developed CKD (creatinine clearance less than 60 mls/min or serum creatinine more than 1.5 mg/dl) and 10.6% of those with proteinuria alone (n=177) developed CKD. Data from 18,912 participants in the Reykjavik Study (19), a mass-screening programme, showed that the crude prevalence of CRF (creatinine more than 150 μmol/l) was 0.22% (220 per 100,000 population). Due to the difficulty in interpreting follow-up data, it is not possible to state how many of those with CKD went on to develop ERF.

One Dutch mass-screening programme (22) showed that 6.6% of the screened general population had microalbuminuria, and that those with overt proteinuria had depressed creatinine clearances. The full follow-up results were awaited at the time of writing this document.

A mass screening of 14,082 subjects in Bolivia identified only 11 with CKD after 3 years of follow-up (20). This study however does not give its criteria for defining CKD.

Two studies (9, 10) reported the results of a mass-screening programme for Australian Aborigines. Aborigines with urine albumin creatinine ratio of more than 3.4 were found to be at higher risk for end-stage renal failure, and both all-cause and renal deaths (9). The authors have not defined ERF in their study. Treatment initiated with ACE inhibitors in high-risk patients found on screening, resulted in reduction of both all-cause and renal deaths (10). The number needed to treat for preventing one all-cause natural death was 11.6.

Studies in the paediatric population

One paper (18) has reported the screening programme for children in Taiwan aged between 6 - 15 years. Children had dipstick testing of their urine twice a year. Data was presented for 10,288,620 students screened and followed continuously between 1992 and 1996. 0.3% of the 2.7 million children screened had a positive test (haematuria, proteinuria or glycosuria). The absolute number and percentage of patients with heavy proteinuria was found to decrease annually. Importantly, there was a decrease in children on dialysis due to glomerulonephritis from 63.2% in 1992 to 47% in 1997. The correlation between the decrease in children with heavy proteinuria and those on dialysis was significant (p less than 0.05)

One study (4) reports a screening programme with routine urine dipstick testing for children in South Korea. Between 1998 and 2000, 452 children were found to have abnormal dipstick results, out of which 173 (38.2%) had kidney biopsies. 169 (36.9%) of all the investigated children were found to have a variety of problems such as IgA Nephropathy and various glomerulonephritidies. The study has several drawbacks. The authors do not give the total number of screened children, hence the proportion detected and hence the value of the screening could not be established. Whilst a variety of pathologies were identified by biopsy, no data is presented on the renal function, which would have had a greater practical significance. There are few data in this paper to help decide whether using a screening programme for renal diseases amongst school children would be beneficial.

Pugia's study (21) was more helpful. The prevalence of suspected nephritis amongst school children in Japan on mass urine dipstick testing was estimated to be 35 cases per 100,00; for persistent proteinuria this figure was 66 and for urinary tract infection it was 61.

Screening patients with known renal risk factors

One study (7) that screened patients with known diabetes and hypertension found that 8.4% had elevated serum creatinine and 3.9% had significant proteinuria. An audit (17) of screening of patients with diabetes and/or hypertension in 12 general practices in London found that, based on a creatinine of more than 125μmol/l, the prevalence of renal insufficiency in this population was 110,000 per million population.

One paper (24), based on retrospective data of 19 patients with biopsy proven HIV associated nephropathy, has found that CKD (more than 100 mg/dl proteinuria or serum creatinine more than 1.5 mg% on at least two consecutive occasions one month apart) was present in nine of them for more than 12 months before the biopsy, and hence screening of patients with HIV for CKD may uncover renal insufficiency at an earlier stage.

Screening relatives of patients with known renal risk factors or renal disease (diabetes, hypertension, etc)

The Kidney Early Evaluation Programme (KEEP) study was reported by Brown et al (2). This study screened volunteers in 21 cities in the USA who had first order relatives with diabetes, hypertension or kidney diseases and those with a personal history of diabetes or hypertension. Out of 889 individuals screened, 42.9% were found to have markers of kidney disease (microalbuminuria, haematuria, pyuria, raised serum creatinine). 22% of the screened population visited their physician within three months of the screening.

In the study by Butkus (3), out of the 335 patients referred for renal transplantation, 30.6% of the African Americans and 25% of Caucasians had at least one first- or second degree relative who had end-stage renal disease. These figures exclude patients with known hereditary conditions such as adult polycystic kidney disease. Of 221 patients with family history of ERF, 49.3% had creatinine clearance of less than 90 mls/min and 13.9% had creatinine clearance less than 60 ml/min (15).

Data based on models

Craig et al in Australia (6) have estimated that 20,000 people aged over 60 years would have to be screened to prevent one case of ERF. And to achieve this 100 people would have to be treated with ACE inhibitors. Depending on treatment effects of antihypertensive agents, screening of diabetic patients for microalbuminuria will produce a reduction in the need for dialysis and transplantation by 21% to 63% and life expectancy increase will be between 4 and 14 years (1). Another study (16) based on a model of screening for nephropathy in insulin dependent diabetic patients showed that 423 patients would have to be screened for 10 years to prevent one year of dialysis, and treatment with ACE inhibitors at the start of microalbuminuria must delay macroalbuminuria by 1.6 years to be cost-effective.

Summary statements

- There is currently no data on screening of the normal population in the UK.
- Whilst screening programmes in other countries that are community based and also those that are targeted at high-risk populations do identify both patients with CKD and those at risk of developing CKD, it is still unclear whether they are effective or cost-effective in the long-term. (Level 2)

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Question 6

What is the risk of CKD in patients with urinary stone disease? Are patients who have presented with urinary stone disease at risk of developing renal impairment? (and would they therefore benefit from follow-up?)

Comments on the evidence

Most people who experience an episode of kidney stones will have at least one recurrence and some will suffer repeated bouts. Renal stone diseases may affect the kidneys in several ways. The stones themselves may scar the renal tissue and act as a focus for infection. The underlying diseases that cause renal stone formation, and the treatment for renal stones, may both actually damage the kidneys in the long run.

The proportion of patients developing renal impairment differs according to the type of kidney stones ie its chemical composition and underlying aetiology. In one study (7) of recurrent idiopathic calcium stone formers, 18% patients were noted to have renal impairment. 30% patients with stag-horn calculi have been found to have abnormal creatinine clearance (5). Although the risk for renal impairment is high in patients with cystinosis, ERF develops in less than 5% of the patients (6). Almost 80% of patients with primary hyperoxaluria develop ERF before 40 years of age (9). In patients with kidney stones due to Type 1 Renal Tubular Acidosis, the annual incidence of ERF is only 0.23% (Wrong 10).

Two short-term studies have shown that anatrophic nephrolithotomy and extracorporeal shock wave lithotripsy (ESWL), which are used to treat renal stones, reduce GFR by 10% and 5% respectively (3, 4).

One case control study (8) has shown that history of kidney stones is associated with increased odds of developing CKD (Odds Ratio 1.9, 95% Confidence Interval 1.1 to 3.3). After stratification by hypertensive status, this increased risk was found to be significant only in patients with no history of hypertension.

One review article (2) has identified female sex, struvite stones, presence of conditions favouring urinary tract infection, anatomic abnormalities of the urinary tract, single anatomical functional kidney and transplanted kidneys, as risk factors for renal failure in patients with kidney stone disease.

No studies were found to assess the long-term benefits of follow-up of patients with kidney stones, especially with regards to renal function.

Summary statements

- Kidney stones are associated with a small risk of developing CKD. The risk varies according to the different types of stone and the underlying factors that predispose to stone formation. (Level 3) (1, 5, 6, 7, 8, 10)
- There is currently no evidence that looks at the renal function benefits of long-term follow-up of patients with kidney stones.

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Question 7

How early should people with CKD be referred to a nephrologist? ie what is the evidence for early vs more delayed (but not late) referral?

Comments on the evidence

Early identification of patients with CKD is important both to offer interventions that may slow the progression of disease to ERF, and also to treat associated comorbid conditions, mainly cardiovascular disease.

Adverse consequences of late referral of patients with CKD have been studied extensively. However, studies that assessed the benefits of early referral were hard to come by. Importantly, none of the studies assessed the level of glomerular function at which referral to the nephrologists resulted in improvement in both survival and preservation of renal function.

One study was excluded, as it was a duplicate paper (15).

Of the included studies, five were from Europe (3, 4, 6, 9, 11,), three from UK (7, 8, 13), five from USA (1, 2, 5, 10, 12) and one from Taiwan (14).

All the included studies determined 'early' or 'late' referrals by determining the time between referral and start of dialysis. One study assessed it by using the number of nephrology visits prior to start of dialysis (11). Late referral was variously defined as referral to renal services less than 1 month (6, 10), less than 90 days (2, 4, 13) , less than 16 weeks (9), less than 4 months (1, 5, 7, 8, 12), less than 6 months (3, 14), and less than 3 visits to the nephrology clinic (11), prior to start of dialysis.

Benefits of early referral

One study (4) showed that early referral was associated with better metabolic status, a higher likelihood of pre-dialysis transplantation and shorter hospital stay at start of dialysis. Type 2 diabetic patients referred early to the nephrologist were found to have lesser risk of death and dialysis technique failure (14). Sirignano et al (11) have reported that early referral was associated with wider use of erythropoietin and ACE Inhibitors.

Adverse consequences of late referral

Several studies (2, 5, 6, 7, 8, 12, 13) have shown that patients referred late have higher mortality rates compared to those who are referred early. However, other studies (3, 7, 9, 10) did not find any difference in mortality between late and early referral patients. At start of dialysis, those referred late were found to be less likely to have 'poor metabolic status' (low haemoglobin, low albumin, high phosphate levels) (1, 3), functioning permanent vascular access (1, 3, 7, 8) and to receive a kidney transplant 1 year after start of dialysis (6, 8. Patients referred late were noted to have longer hospital stay at the start of dialysis in two studies (4, 8). Roderick et al (7, 8) found that patients referred late had not received standard therapies such as erythropoietin, phosphate binders and cardiovascular prophylaxis such as aspirin and lipid lowering treatment.

Summary statement

- The studies had no consistent way of dividing the population of patients, as none used a specific GFR value. Thus excluding patients referred 'late' (defining that as those requiring preparation for

dialysis including treatment of anaemia and bone disease), there is no guide from the evidence for the level of GFR at which patients benefit from being referred to a nephrologist.

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Question 8

Is there a consensus on the management of solitary kidneys (congenital/surgical donors)?
Is there any long-term risk for kidney donors?

Comments on the evidence

Two studies were excluded due to poor patient selection and unclear data presentation (15, 16).

Five studies were from Europe (3, 4, 7, 8, 12), three were from the USA (1, 2, 5), one from the UK (10), one from Canada (9), one from Chile (14), one from Japan (6) and one from Egypt (11).

Solitary kidney due to congenital abnormalities and surgical causes other than donor nephrectomy

A study (1) of 95 patients with unilateral renal agenesis (URA) showed that these patients had increased risk of proteinuria, hypertension, and renal insufficiency. The findings of this study are limited by the fact that it had follow-up data from only a third of its original study population of 157 patients.

31 patients who had uninephrectomy in adulthood due to unilateral renal diseases, when followed-up more than 20 years after the surgery, showed mean creatinine clearance levels that were 92.9% of that in age-sex matched healthy controls (Ohishi 1995). However, another study (7) showed basal creatinine clearance was significantly lower in patients who had uninephrectomy more than 10 years ago, when compared to healthy controls (mean creatinine clearance 45.3 vs 103.1). 27 patients who had uninephrectomy as children, examined after a mean of 23 years post-nephrectomy, were shown to have a mean of C_{cr} of 83.5 ml/min (9). This value was 74% of that of a healthy control population.

Regazzioni et al (8) performed a study to determine the 'renal reserve capacity' in 37 patients who had uninephrectomy as children. Renal reserve capacity was calculated as the relationship between baseline GFR and maximal stimulated GFR following oral protein load. This study showed that patients with uninephrectomy more than 11 years ago had significantly lower renal reserve capacity than healthy controls. It should however be noted that their baseline GFR did not differ from that of normal controls, and that the clinical significance of 'renal reserve capacity' is yet unknown.

Wikstad et al (13) studied 36 patients who either had uninephrectomy as children or were born with URA. He found that the GFR was significantly different from the control population only in those in whom the follow-up period was longer than 25 years.

Although patients with solitary kidneys due to congenital problems or nephrectomy for reasons other than kidney donation had reduced GFR, their renal insufficiency was not of a degree that could be termed conventionally as CKD or uraemia. It is important to note that all the patients assessed in the studies mentioned here had normal contralateral kidneys and had no ongoing problems that would impair functioning of that kidney.

Living kidney donors

The data on the post-transplant period in the studies assessed are given in Table 1:

Table 1

Post-transplant duration

Study	**No. of years since kidney donation**
Conrad	All patients more than 10 years
Fehrman-Ekholm 1997	All patients more than 20 years
Fehrman-Ekholm 2001	Range 2 to 33 years
Najarian	All patients more than 20 years
Saran	Range 1.4 to 21 years
Sobh	Range 1 to 10 years
Talseth	Range 9 to 15 years
Undurraga	Range 1 to 21 years

The issue of long-term complications of kidney donation has been addressed in Question 17 of The Evidence Base for Part One of The National Service Framework for Renal Services (2004). Living kidney donors were found not to have any long-term adverse effects such as decreased survival or renal insufficiency. Two studies (3, 5) retrieved for this review have already been assessed and included in our earlier review and the findings of those papers have not been repeated here. The evidence from the studies newly identified for this question was in keeping with the findings in our previous review of this topic. Although living kidney-donors had increased incidence of proteinuria (4, 2, 10, 11, 12, 14), there was no evidence of renal insufficiency (4, 2, 10, 11, 12, 14) as assessed by serum creatinine and creatinine clearance levels. The risk of developing hypertension in living kidney donors was not higher than that of the general population matched for age in some studies (4, 11), but others studies have reported an increased prevalence of hypertension (10, 12, 14). None of the studies have noted an increase in the incidence of CKD in the living kidney donor population.

Summary statements:

- Patients who undergo uninephrectomy with contralateral normal kidneys and no systemic diseases that might cause renal insufficiency at the time of nephrectomy had slightly reduced GFRs, but were found to have stable renal functions, over follow-up periods of up to 23 years. (Level 3) (9)
- Living kidney donors do not have any long-term renal adverse effects. (Level 3) (4, 2, 10, 11, 12, 14)

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Excluded studies

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Question 9

Has any intervention (such as ACE inhibition) been shown to be useful in slowing progression of CKD in children or during adolescence?

Comments on the evidence

One study (7) was excluded as it did not address the topic in question and the other (8) because it was only a description of an ongoing trial.

Of the included studies, one was from Chile (1) and five were from Europe (2, 4, 3, 5, 6).

One retrospective study (5) (48 children, follow-up – 8 weeks) found that enalapril alone and enalapril combined with prednisolone had significantly greater reductions in proteinuria in normotensive proteinuric children. The reduction in proteinuria was not related to the patient's blood pressure. Enalapril produced a decrease in proteinuria in children with Alport's syndrome, but this was also accompanied by a reduction in GFR (3), (5 patients, follow-up 2 years). ACE inhibitors were also found to be effective in reducing microalbuminuria in children with reflux nephropathy (2) (16 patients, follow-up 2 years). ACE inhibitors in 14 children with hypertension were found to reduce albuminuria in nine of the 11 patients who had increased albumin excretion (6) (follow-up 26 weeks). Enalapril, when given to six children with nephrotic syndrome from a variety of causes, resulted in a significant decrease in proteinuria in two children and a moderate decrease in proteinuria in three (4) (follow-up 24 months). In the study by Delucchi et al (1), out of 12 children only 2 were completely free of proteinuria at the end of study period (48 months).

Only the Sasinka (5) study had a control group. In general, all the studies had very few patients.

Summary statement

- The studies on the use of ACE inhibitors to slow CKD are very small and inconclusive. Further multicentre research would be of value.

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Excluded studies

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Question 10

Do interventions (such as ACE inhibition) work before there are overt signs of kidney disease such as microalbuminuria?

Comments on the evidence

Three studies (11, 13, 14) were excluded, as they were only a description of an ongoing trial. Three were excluded as they were duplicate papers (7, 8, 9, 12). Two studies were excluded as they included a population consisting of patients with both covert and overt renal disease (15, 16). Two papers (9, 10) did not deal with the topic in question and were therefore excluded.

Of the seven included studies, one was from Denmark (5), one from Israel (7), one from Sweden (3), one from the USA (2) and three were multinational studies (1, 4, 6).

Studies with normoalbuminuric patients only

Ravid et al (7) in their study (156 patients, follow-up 6 years) showed that in Type 2 diabetic patients who were normoalbuminuric, enalapril in comparison with placebo reduced the risk of developing microalbuminuria by 12% and significantly reduced the decline in creatinine clearance ($p = 0.04$).

The Heart Outcomes and Prevention Evaluation (HOPE) study (4) evaluated the use of ramipril, an ACE inhibitor, in patients who were at high risk of cardiovascular events. Men and women who were at least 55 years old were eligible for the study if they had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria).

Analysis of data from a subset of 6,055 patients in the HOPE study, who had no albuminuria or microalbuminuria at baseline, showed that ramipril in comparison with placebo reduced risk of developing proteinuria (defined as new microalbuminuria or new clinical proteinuria/overt nephropathy) (Odds ratio 0.85, 95% CI 0.75 to 0.97) (6). However amongst the subgroups of diabetics in the same population, the risk reduction was not significant ($p=0.017$) (4, 6).

Whilst normotensive, normoalbuminuric Type 1 diabetic patients (n=89, follow-up 3 years) on placebo had significant increase ($p=0.007$) in their Albumin Creatinine Ratios when compared with those on ramipril, there was no difference in GFR at the end of the study period (5).

Studies including patients who had microalbuminuria

The EUCLID study (1) (530 patients, follow-up 24 months) showed that lisinopril, when compared with placebo, reduced the albumin excretion ratio (AER) by 12.7 % ($p=0.1$) in normoalbuminuric patients and by 49.7% in the microalbuminuric Type 1 diabetic patients. This study also showed that in baseline AERs of 5μg/min or less there was no significant benefit with lisinopril therapy.

In patients with both Type 2 diabetes and hypertension, sub analysis of the rate of decline of creatinine clearance in patients with normo- or microalbuminuria was not different between those achieving moderate (diastolic blood pressure 80-89 mm Hg) or more intensive reduction (diastolic blood pressure less than 75 mm Hg) in blood pressures, and also between those on ACE inhibitor (Enalapril) or Calcium Channel Blocker (Nisoldipine) (470 patients, follow-up 5 years) (2).

One study (3) (257 patients, follow-up 24 months) compared the ACE inhibitor Cilizapril with the beta-blocker Atenolol in hypertensive patients with normal GFR. Patients in both drug groups did not differ in the rate of decline of GFR. GFR decline in this study was not related to the reduction of systolic blood pressure.

Summary statement

- There is some suggestion from three studies (2 of diabetics and one including diabetics and non-diabetics) that in patients with normal albumin excretion, ACE inhibitors do prevent the development of new microalbuminuria and reduce the rate of decline of creatinine clearance (6, 7) (Level 1). Since the non-diabetics all had history of cardiovascular disease, the results cannot be extrapolated to the general population.

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ACUTE RENAL FAILURE

Question 11

Are there any significant health trends within populations that will significantly influence incidence of ARF and the epidemiology, eg social deprivation, age distribution, ethnic grouping, CHD and vascular disease, HIV, infectious disease, hospital-acquired infection such as MRSA?

Comments on the evidence

Although a common serious condition, relatively little is known about the epidemiology of (ARF) when compared with chronic end-stage kidney disease. Feest (1) studied patients who developed ARF from a population base of 450,000 between 1986 and 1988 and showed the incidence of ARF be 140 per million of the population (173 per million/population). A patient with ARF was defined as having a serum creatinine above 500μml/L when first measured which then returned to below that level and remained there; ARF was also said to have taken place if the patient died during the acute illness and the history or necropsy confirmed ARF. Patients whose ARF complicated a terminal illness were excluded. The numbers receiving dialysis for ARF were 18 per million of the population (22 per million/population).

Liano, in a study which recruited patients between 1991 and 1992, reported an incidence of 209 per million of the population in his study of 13 tertiary care centres serving a population base of 4 million in Spain (2). 57 patients per million/population were dialysed. ARF, however, was defined somewhat differently and included patients with less severe renal failure. He included patients who had a rise in serum creatinine of greater than 177μml/L if there had been previous normal function; those with an elevation of serum creatinine on admission with 100% recovery, or a 50% recovery if the clinical conditions suggested ARF, were also included. Stevens et al (4) prospectively studied patients with ARF defined as a temporary rise in serum creatinine to more than 300μml/l. They also studied patients with renal failure using Liano's definition. They found the incidence of ARF to be 545 pmp including those with ARF occurring in relation to a terminal illness and those with acute on chronic renal failure.

The differences in definitions make this a complex area to investigate and also make it difficult to compare the results of different studies. Currently work is underway as part of the Acute Dialysis Quality Initiative to try to define and classify ARF so that optimal management guidelines for patients can be developed and monitored (3).

Even when taking a crisp criterion like the requirement for RRT, results of studies may still not be comparable because the ability to treat may depend upon the availability of RRT. Furthermore, those who develop a sudden rise in creatinine on a background of already impaired renal function may be included to a greater or lesser extent in different studies. Recent studies (4, 5, 6) which recruited patients in the mid to late 1990s showed a wide range of rates of 93, 176 and 203 per million/population for those receiving dialysis for ARF.

Whatever the limitations of the studies, however, the numbers receiving RRT for ARF has risen dramatically over a 15 year period. Several studies show that ARF is more frequent in the elderly (1, 4, 7), one (7) showing an incidence of 157 pmp in the age group 20-49 and 2,694 pmp in the age group 70-79 years. Comorbid illness, particularly cardiovascular disease, was commoner in those with acute on chronic renal failure (4).

Studies vary in the way they define the causes of ARF. Many patients have several reasons for developing ARF. For example, dehydration and sepsis occurring following surgery. One study recorded sepsis as contributing to ARF in around 25% of patients (4), and another, studying those requiring RRT only, indicated that 69% had evidence of sepsis(6) and 25% were post-operative.

In the main, conditions primarily affecting the kidney are relatively unusual causes of ARF. Liano records 48 of 748 patients studied as having primary renal disease (2). Many patients have multi organ failure and develop ARF in hospital as a secondary event to a variety of primary stimuli.

Summary statements

- Relatively little is known about the epidemiology of ARF compared with chronic end-stage kidney disease.
- The numbers of developing ARF have risen sharply over the past fifteen years.
- Comparison of epidemiological studies is made difficult because of differences in definitions of ARF.
- The majority of patients with ARF develop it secondary to other conditions.
- Sepsis is a very common precipitating factor for ARF.
- ARF can occur on a background of chronic renal impairment.
- Older patients and those with cardiovascular disease are more likely to develop ARF.

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Question 12

What impact does early identification of patients with a background of CKD, and those with an acute deterioration in renal function, have on management, treatment and outcome for different groups of patients eg

- those identified pre-operatively (eg during pre-admission assessment) as an elective patient
- those identified on admission to hospital as an acute/ emergency medical or surgical patient
- during hospital stay eg critical care outreach services and early warning systems?

Comments on the evidence

No studies were identified that assessed the impact/change in management, treatment or outcome following identification of different groups of patients with pre-existing CKD or acute deterioration in renal function.

The search identified several studies that have described factors associated with development of ARF in certain specific settings such as cardiovascular surgery, and also the impact of ARF on outcomes such as survival and hospitalisation. For assessment of effect of ARF on survival and hospitalisation, studies have only been included that have compared outcomes in patients with ARF against those with normal renal function.

Of the included papers, nine were from the USA (2, 4, 5, 10, 11, 12, 15, 16, 17), seven from Europe (1, 3, 6, 7, 8, 18, 20), two from the UK (9, 14), one from Australia (13) and one from China (19).

Several studies have found that ARF is an independent predictor of mortality. In patients developing ARF not requiring dialysis, mortality has been reported to range from 4.2% (13) to 44.4% (20). In patients developing ARF requiring dialysis, mortality rates range from 28% (5) to 64% (4). Patients with ARF have also been shown to have a longer ITU (12, 20) and hospital (7, 13, 12) stay, when compared with those with normal renal function.

One study (15) from the USA assessed the effect of delayed nephrology consultation in patients with ARF in the Intensive Care Unit (ICU). Delayed consultation was defined as $\geq$ 48 hours interval between onset of ARF and nephrology consultation. This study found that while delayed nephrology consultation had a statistically non-significant association with increased mortality, it had a significant association with increased ICU stay (17 days vs 6 days, p less than 0.0001) and length of hospitalisation (median, 19 days vs 16 days, $p = 0.01$).

Pre-existing renal impairment is one of the most important factors in the development of ARF. In a surgical setting pre-operative elevated serum creatinine has been associated with ARF (1, 4, 7, 9, 10, 11, 13, 12, 18, 19, 20). A systematic review of 28 studies involving 10,865 patients undergoing surgery found that the most consistent pre-operative factor contributing to ARF was pre-existing renal impairment (17). One study (2) has found that pre-existing CKD was significantly associated with the development of ARF in patients in the ICU setting. Hospital acquired renal insufficiency was more common in patients with pre-existing renal impairment (16). In one community based study (14), almost 20% of patients requiring RRT for the first time had acute on chronic renal failure.

Risk factors for ARF other than pre-existing CKD have also been identified. Advanced age has been found to be a risk for ARF in patients in ICU (2, 6), and in those undergoing cardiovascular operations (1, 4, 5, 10, 12, 13, 19, 20). In patients undergoing cardiovascular operations, pre-operative factors associated with increased risk of developing ARF include diabetes mellitus (4, 9, 10, 12, 19), hypertension (10, 18), reduced left ventricular ejection fraction (4, 5, 8, 10, 12), chronic obstructive pulmonary disease (4) and congestive cardiac failure (19). Intra- and perioperative factors associated with development of ARF include use of intra-aortic balloon pump (4, 20), increased cardiopulmonary bypass time (5, 9, 12, 20), and

postoperative hypotension (20). In patients undergoing orthotopic liver transplantation, 'standard' technique, which involves retroperitoneal tissue dissection as opposed to 'piggy back' technique, is associated with a greater risk of postoperative ARF (3).

Whilst there are no studies assessing benefits of early identification of patients with pre-existing CKD or those with acute deterioration of renal function, considering the mortality and morbidity associated with ARF a vigilant attitude is required for those patients in whom risk factors such as the ones found above are noted to be present.

Summary statements

- There are currently no studies looking at the effectiveness of early identification of patients with pre-existing CKD or acute deterioration of renal function.
- ARF is associated with increased mortality (4, 13, 12, 20), and longer ICU (12, 20) and hospital stay (7, 13). (Level 3)
- Delayed nephrology consultation for patients with ARF in the ICU has a significant association with length of hospitalisation and ICU stay. (Level 3)
- Pre-existing CKD has been identified as the most consistent factor contributing to the development of ARF in postoperative patients. (Level 3) (17)
- Several other risk factors for development of ARF following surgical procedures, especially cardiovascular operations have been identified such as age (4), diabetes mellitus (4, 9) and reduced left ventricular ejection fraction (4, 5, 8). (Level 3)

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Question 13

What is the impact of the use of protocols for the prevention of deterioration of ARF on

- the incidence of established ARF needing RRT
- the clinical outcome?

Comments on the evidence

Patients may be at risk of developing ARF, for example following major surgery or during any major intercurrent illness, particularly if they have background renal impairment. Certain preventative measures may be appropriate such as the avoidance of infection and care with fluid balance. In addition, once ARF has developed it may be possible, perhaps by the use of protocols, to improve the clinical outcomes. Studies were searched for that looked at the use of protocols in improving outcome in these two areas [a) and b)]. Very little published evidence was found regarding the utility of protocols.

One UK study (2) demonstrated that the use of a nutritional protocol for patients with ARF improved the uptake and administration of nutritional therapy, but this did not translate into significantly improved patient survival or renal recovery. Cost analysis was carried out and costs were little different before and after the use of the protocol. A further study from the USA (3) compared the number of patients developing ARF following cardiac surgery before and after the development of a new protocol for the care of patients at high risk of renal failure. Following the adoption of the protocol, fewer patients developed ARF, although the study included no clinical outcomes data, eg patient or renal survival. Research in the UK (1) showed that the use of a protocol for the administration of fluids and electrolytes during haemofiltration allowed trained nurses in the ICU to respond more rapidly to changes in patients' acid base and electrolyte status during haemofiltration. Again information on patient outcomes was not given. A further study, again from the UK (4), estimated that a significant proportion of ARF was preventable and hence felt that guidelines could help in management.

Summary statements

- Few studies were found.
- No studies were found showing the influence of the use of protocols in ARF on patient outcomes.
- Using protocols may improve management of nutrition, fluids and electrolytes for patients on haemofiltration. (Level 3) (1, 3)
- Identifying patients at high risk for ARF after cardiac surgery and using protocols for their post operative fluid and haemodynamic status management may lead to decrease in ARF in that population. (Level 3) (2)

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3. Page US, and Washburn T. Using tracking data to find complications that physicians miss: The case for renal failure in cardiac surgery. Journal on Quality Improvement 1997; 23 (10): 511-20
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Question 14

Are there organisational models, such as prevention protocols, that improve early detection and intervention for ARF?

Comments on the evidence

No specific papers were found which dealt with this issue. A North American study by Page et al (1) showed that the use of a special software called 'Runs analysis' pointed to a trend for increasing incidence of ARF post operatively in patients following cardiac surgery over time. In some centres, medical staff had failed to notice this rise. The use of this software allowed increased detection of ARF in the selected population and, also helped point towards the likely aetiology. In the UK, some hospitals have 'outreach teams' often based in ITU, which advise on patients in other wards in the hospital. One of their aims is the prevention and early detection of ARF. No published evidence was found on this topic.

Summary statement

- insufficient evidence is available to make a clear statement for the use of protocols. Common sense might suggest that in several situations they might be useful.

Reference

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Question 15

Are there organisational models that improve outcome for ARF?

Comments on the evidence

Patients with ARF who require RRT can be treated in several locations. Some require to be in ICUs for other reasons, such as the necessity for artificial ventilation, and hence dialysis or haemofiltration is undertaken there. In ICU they may be managed by intensivists or by a combination of intenstivists and nephrologists. Others are treated in renal units or wards by nephrologists. In the UK many large hospitals do not have a nephrology service and rely on regional renal units. These hospitals however do have ITUs where RRT, particularly haemofiltration which requires less technical expertise than haemodialysis, can be carried out. In hospitals in many countries where there are both nephrologists and intensivists, practice varies. In some countries, patients who come to ITU for other reasons may have RRT carried out by intensivists; in other hospitals nephrologists are involved. Several models of care for RRT in ARF therefore exist.

Few studies were found which addressed the issue of the optimal model of care.

Barton (2) showed that of 50 patients treated at Whipps Cross Hospital (a district general hospital) 3 of the 21 patients predicted to survive, died, and 10 out of the 29 patients predicted to die, survived. The predictions were based on a scoring system developed at the regional renal unit at St Thomas's hospital. The authors concluded that, with appropriate support, patients with ARF can be managed with good outcomes using haemofiltration in the district general hospital setting. Three other studies from the USA and Australia focused on the differences between 'closed' and 'open' ICUs. In the former patients are treated by ICU staff who seek consultation with other sub-specialists as they feel appropriate. In the 'open' units the patient is under the care of the referring physician, although intensivists are present and other specialists, particularly nephrologists for the care of ARF, are more fully involved. These systems have grown up largely for logistic and financial reasons in different countries. In the 'closed' ICUs, particularly in Australia, continuous RRT is almost exclusively used to treat ARF. Two papers (3, 4) described 'open' and 'closed' units, the former being the more common model in the United States and the latter in Australia. The perception that 'closed' units are associated with such 'excellent patient outcomes' persuaded the Australian authors that it would be impossible to conduct randomised studies comparing intermittent with continuous therapies. A further study carried out in the United States (5) compared outcomes before and after the change from an 'open' to a 'closed' system of delivering intensive care. They found, although the methodology was not very robust, that outcomes were slightly better after having changed to the 'closed' system. It is difficult however to exclude the fact that other changes over time might have caused the improvement.

Summary statements

- Relatively little evidence was available to help address this topic. Only one study was available from the UK.
- There is no strong evidence at present to support one particular model over another. 'Open' and 'closed' units are perceived by staff to be successful, and in the UK dialysis in an ICU outwith a regional renal unit appears also to be satisfactory.

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Question 16

Does early RRT in ARF improve outcomes?

Comments on the evidence

No well-designed clinical trial has demonstrated benefit from early RRT in ARF. Studies that have indicated benefit from early intervention (1, 2, 3, 4) all risked serious selection bias. One well-designed RCT (1) found no difference in outcome between early and late RRT. One of the difficulties in summarising data from these trials was the different definitions of early and late; in some studies it was time in ICU, in others it was time from development of a defined level of renal impairment. Two other RCTs were identified (2, 3) which, though not addressing the exact question, are relevant to this area. Cole et al (2) found no evidence that early continuous venovenous hemofiltration in patients with septic shock improved clinical outcome measures or the removal of cytokines. Durmaz et al (3) found a survival benefit with pre-operative dialysis and early post-operative dialysis for patients with moderate pre-operative CKD undergoing Coronary Artery By-pass Grafting. In this study, the in-hospital mortality for the early dialysis patients was 4.8% (1 out of 21 patients) compared with 30.4% (7 out of 23 patients) for the control patients. This study needs to be repeated but may have important lessons for the pre-operative management of patients with moderate CKD due to have Coronary Artery By-pass Grafting.

Summary statements

- ARF particularly in ICU patients carries a high mortality of approximately 50%.
- Early RRT does not improve survival or other outcome measures.
- There is no evidence that early RRT is harmful.
- Pre-operative dialysis for patients with moderate renal impairment needs to be further evaluated.

References

Included Studies

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Excluded studies

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Question 17

Do continuous versus intermittent dialysis techniques improve outcome in ARF?

Comments on the evidence

The search strategy generated 766 references after duplicate references found by more than one database were removed. A total of 13 papers were considered for further review. Out of the 13 papers, one was excluded (9) as it reproduced the same data as another paper, three were excluded because of methodological issues (7, 12, 15), five did not deal with clinical outcomes (8, 10, 11, 14, 16) and one study was excluded as it only compared two intermittent modalities against each other (13).

Six papers were considered eligible for inclusion. Two were from the USA (4, 5), one from Canada (6), two from the UK (1, 2) and one from the rest of Europe (3). Two were systematic reviews (4, 6).

The systematic review by Kellum et al (4) considered a total of 13 studies of which only 3 were RCTs and none of these were published other than in abstract form. In only 6 of the 13 studies were baseline characteristics similar in both study groups. Analysis of these studies showed that continuous RRT was associated with improved hospital mortality when compared with intermittent RRT. There was no significant reduction in mortality when all 13 were included in an adjusted comparison. However, when adjusted for study quality, similarity of baseline severity of illness, or both, the overall effect was in favour of continuous RRT.

The systematic review by Tonelli et al (6) assessed six RCTs and 12 non-RCTs. The analysis of six RCTs did not show any difference in mortality between Intermittent Haemodialysis and continuous renal replacement groups. The results were unchanged even by including non-RCTs in the analysis or by controlling for baseline differences in illness severity. There was also no difference between modalities as far as renal death or likelihood of dialysis dependence was concerned. This paper in fact points to several flaws in the systematic review quoted previously (Kellum 2002) such as non-inclusion of several RCTs and use of statistical tools that would not adjust for study differences. The authors of this paper therefore do not agree with the conclusion that continuous renal replacement confers survival advantages in patients with ARF.

One prospective observational study (3) found that in-hospital mortality was greater in the continuous RRT group than in the intermittent RRT group. A multivariate analysis of the data however found that outcome was not independently associated with dialysis modality. A RCT from the USA (5) looked at ARF requiring dialysis in the ICU population. This study did not show any difference between Intermittent Haemodialysis and continuous RRT as far as patient survival and renal recovery were concerned. Two papers from the UK (1, 2) showed that Intermittent Haemofiltration was associated with increases in Intracranial Pressure in patients with acute hepatic and renal failure when compared with Continuous Arteriovenous Haemofiltration or Continuous Haemofiltration with Dialysis.

Summary statements

- Continuous RRT does not appear to have an advantage over intermittent RRT in treating patients with ARF. (Level 1) (3, 5, 6)
- Continuous RRT may be beneficial in treating ARF in patients at risk of having impaired cerebral autoregulation at risk of cerebral oedema as in those with combine acute hepatic and renal failure. (Level 1) (1, 2)

References

Included studies

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6. Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. American Journal of Kidney Diseases 2002; 40(5): 875-85

Excluded Studies

7. Bunchman TE, McBryde KD, Mottes TE, Gardner JJ, Maxvold NJ, Brophy PD. Pediatric acute renal failure: outcome by modality and disease. Pediatric Nephrology 2001; 16(12): 1067-71
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Question 18

Does the type of membrane used in RRT affect the outcome in ARF?

Comments on the evidence

ARF in the hospital setting is associated with considerable high morbidity and mortality. The mortality is in excess of 50% when the ARF is severe enough to necessitate dialysis treatment (7). Dialysis membranes can be described as biocompatible or bioincompatible. Bioincompatible membranes are mainly cellulose-derived membranes and have a tendency to elicit inflammatory responses on coming into contact with blood. Modified or substituted cellulose membranes such as those made from cellulose acetate are associated with a lesser inflammatory response. The inflammatory responses are said to be associated with adverse haemodynamic changes. Biocompatible membranes are mainly synthetic (Polysulfone, Polyamide, Polymethylmethacrylate and Polyacrylonitrile) and incite substantially less of an inflammatory response. ARF outcome is likely to be affected by several factors including co-morbidity, dialysis modality and dialysis membrane. This review was undertaken to establish whether the type of dialysis membrane used for dialysing patients with ARF affects clinical outcome.

The search strategy generated 462 references after duplicate references found by more than one database were removed. A total of 90 papers were ordered for further appraisal. Two systematic reviews (3, 10) and ten primary studies (1, 2, 4, 5, 6, 7, 8, 9, 11, 12) were considered eligible for inclusion. There was one study from the UK (4), four from the USA (2, 3, 10, 11), one from Brazil (9), one was a combined paper from the UK and New Zealand (12) and the rest from Europe (1, 5, 6, 7, 8, 9). One study was excluded, as it did not give a breakdown of the number of patients in the two membrane types that it assessed (13).

Jaber et al (3) carried out a meta-analysis of seven RCTs and quasi RCTs carried out between 1994 and 2000 and compared biocompatible and bioincompatible membranes. They considered all synthetic membranes to be biocompatible and all cellulose-based membranes to be bioincompatible. A total of seven studies were included in their analysis. This meta-analysis did not show any survival benefit for biocompatible membranes over bioincompatible ones. Sub-group analysis showed a non-significant benefit of synthetic membranes over unsubstituted cellulose membranes and of cellulose acetate membranes over synthetic membranes. Using the random effects model the 'number needed to treat (NNT)' in the group treated with synthetic membranes to save one life would have been 12 when compared with unsubstituted membranes. When comparing cellulose acetate membranes with synthetic membranes NNT analysis showed that for every 20 patients treated with a synthetic membrane instead of a cellulose acetate membrane, one additional life would be lost.

In the meta-analysis by Subramanian et al (10) 8 studies were considered. They included all the studies used by Jaber (3) and a further observational study by Neveu in 1996 (6). There was an overall survival benefit with synthetic dialysis membranes when compared with cellulose-based membranes. Significant survival benefit was found only against cellulose (cuprophane) membranes but not against cellulose acetate membranes. This result may be flawed as one study used cuprophane (unsubstituted cellulose) but was classified in this analysis in the cellulose acetate group. Furthermore, the observational study by Neveu (6) showed the strongest positive effect of synthetic membranes. The authors performed a sensitivity analysis to take into account this and some other methodological problems found in other studies and found no significant patient survival benefit from using synthetic membranes. As far as recovery of renal function was concerned, synthetic membranes were no more effective than cellulose-based membranes.

Of the studies not included in the meta-analyses, one study looked at membrane combinations (biocompatible/bioincompatible and high/low flux membranes) (1). This study failed to demonstrate any survival benefit for biocompatible over bioincompatible or high over low flux membranes. In this study, all cellulose-based membranes were considered bioincompatible and synthetic ones biocompatible. The studies by Jones et al (4) and Ponikvar et al (8) compared two synthetic membranes, (Polyacrylonitrile

versus Polysulfone) in the dialysis of patients with ARF and did not show any survival benefit of one membrane over the other. In the former study the membranes were of similar flux; in the latter the polysulfone membrane used had a lower flux.

There were three studies that compared biocompatible with bioincompatible membranes in ARF in the post-renal transplant setting (9, 11, 12). The studies by Woo et al (12) and Romao et al (9) compared cuprophane with Polysulfone membranes. Valeri et al (11) compared cuprophane with Polymethylmethacrylate. They showed that there was no difference between the two types of membranes as far as patient survival, number of dialysis sessions and renal recovery were concerned.

Summary statements

- There is no evidence to suggest that the biocompatibility (synthetic versus cellulose based) of the membrane used for the dialysis of a patient with ARF has any bearing on patient survival or recovery of renal function. (Level 1)
- The use of biocompatible and bioincompatible membranes in patients with ARF following renal transplantation resulted in similar patient and renal survival: there was no difference in the number of dialysis sessions required. (Level 1)

References

Included studies

1. Gasparovic V, Dakovic K, Merkler M, Gubarev N, Pisl Z, Ivanovic D. Place and role of new membranes in multiple organ failure: an advance or rumors. Renal Failure 2001; 23(2): 175-81
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Excluded Study

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Question 19

- What is the impact on outcome of referral of patients with ARF to a renal specialist?
- Is there evidence that could be used to inform the development of a local protocol for referral for specialist advice?
- Do protocols for referral to a renal specialist improve outcomes?

Comments on the evidence

Five studies were identified that were of some relevance to the impact of specialist care on outcomes for patients with ARF (1, 2, 3, 4, 5).

The number of patients with ARF requiring RRT is growing. A study from as far back as 1980 (5) showed that treating renal failure in a unit without an on-site nephrologist had as good results as studies reported for specialist centres. It was not, however, a direct comparison. A further epidemiological study (1) showed that older patients and those with considerable co-morbidity were less likely to be referred to a nephrologist. The outcome for those referred to a nephrologist, even when an attempt was made to control for comorbidity, was better, but this study was uncontrolled and not randomised. Similarly, in an uncontrolled study in the United States (2) referral to a renal specialist was associated with a statistically significant reduction in mortality after adjusting for co-morbidity and the severity of ARF. A study from the UK (4), again uncontrolled, suggested that initial assessment and management of ARF by non-specialists was sub-optimal. An American study published in 2002 (3) also suggested that delayed nephrology consultation was associated with increased mortality and morbidity whether or not dialysis was ultimately required. The authors of this and one of the other studies (1) point out that since they are using observational data it is difficult to know if these findings reflect a confounding patient selection bias, the adverse effects of delayed recognition of ARF, or the benefits of nephrology consultation.

Summary statements

- The impact on the outcome of referral of patients with ARF to a renal specialist cannot be determined at present.
- In the observational studies that reported benefit from referral, the authors themselves realised that the studies were open to various confounding factors, particularly patient selection.
- No evidence was available to decide whether the development of a local protocol for referral for specialist advice would be beneficial.

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Question 20

Is outcome improved by having a system for referral to paediatric nephro-urological services of babies with severe renal abnormalities diagnosed antenatally?

Comments on the evidence

The research strategy generated just 22 references and a total of 14 papers were ordered for further appraisal. None of the ordered papers directly addressed the issue of referral and therefore it was not possible to answer the question posed in this review. One paper from New Zealand described two case reports illustrating the importance of prompt referral of neonates diagnosed antenatally with renal impairment.

Reference

1. Tuthill D, Elder D, Pringle K, Richardson V, Selby R, Robinson R. Posterior urethral valves: failure of antenatal diagnosis. New Zealand Medical Journal 2000; 333-4

Question 21

Does following up patients who experience ARF improve survival and renal survival?

Comments on the evidence

Several potential factors were identified that are associated with poor renal recovery following ARF (see report for Question 23). The issue of the risk of developing ERF following ARF (see report for Question 22) was also addressed and it was found that ARF is associated with a very variable but definite risk of progressing to ERF. However no studies were found that dealt with looking at the improvement in survival and renal function recovery due to following up of patients who had experienced ARF.

Considering the risk for development of ERF in survivors of ARF, follow-up would be sensible at least in the population that is deemed to have factors that are known to be associated with poor renal function recovery.

Summary statement

- Follow-up after ARF may be advised for patients who are found to have factors associated with poor renal function recovery. (Level 4)

Question 22

What proportion of patients with ARF as part of their critical illness will go on to develop ERF without recovery of renal function after the acute renal illness or at a later stage?

Comments on the evidence

It is important to know the proportion of patients with ARF who go on to develop ERF. This is because patients with ERF have increased need for health care resources due to the morbidity associated with ERF and the cost of treating it with RRT. Estimating the number of patients likely to develop ERF following ARF helps to estimate both the additional clinical resources needed, and the potential costs involved.

While examining the publications for some of the other questions it became clear that they also addressed this one. Thus the relevant papers were also included that were retrieved for questions regarding epidemiology, follow-up, and factors associated with non-renal recovery of renal function (questions 11, 21 and 23). A total of 72 papers were assessed.

In order to avoid ambiguity about the criteria/definition of ERF, only those patients requiring RRT following ARF were considered to have developed ERF. The percentages given represent the proportion of survivors developing ERF following ARF.

Excluded papers

A total of 44 papers were excluded.

18 papers (30, 31, 32, 33, 34, 37, 40, 41, 43, 44, 47, 57, 58, 59, 66, 67, 70, 71) were excluded, as they did not deal with outcomes following ARF.

Nine papers (38, 42, 45, 46, 48, 49, 53, 52, 55, 61) dealt with outcomes of ARF, but did not assess renal recovery as part of their outcome measures.

Twelve papers had to be excluded (50, 51, 52, 54, 60, 62, 63, 64, 65, 68, 69, 72) as, although they looked at renal function recovery following ARF, they only reported data as the proportion of patients with complete or partial renal recovery, rather than clearly stating the number of patients who developed ERF and required RRT.

Two papers (56, 73) that did give data on patients developing ERF after ARF were excluded as the data was presented in such a way that the proportion of people developing ERF could not be estimated confidently. Two review papers (35, 36) were excluded as they were not related to the topic in question. One study was excluded (39) as it was a duplicate publication and presented part of the results from a larger study (22).

Included papers

A total of seven papers dealt with paediatric ARF (10, 14, 16, 23, 24, 26, 29) and most of them were concerned with long-term sequelae of haemolytic-uraemic syndrome.

Twenty two papers dealt with ARF in the adult population (1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 15, 17, 18, 19, 20, 21, 22, 25, 27, 28).

There were seven studies from the UK (4, 5, 8, 19, 21, 23, 25), ten from Europe (1, 2, 3, 9, 10, 11, 12, 14, 26, 28), six from the USA (6, 7, 15, 18, 20, 27), one from Argentina (24), one from Australia (22), one from Japan (29) and one from Saudi Arabia (16).

One review article (15) has been included as it gives a table of the proportion of patients developing ERF in a number of studies previously published.

There were four prospective community based studies (4, 8, 13, 19).

Six studies (6, 7, 12, 18, 21, 22) were carried out in an ICU setting.

ARF was defined in 14 studies (1, 2, 5, 8, 9, 11, 13, 16, 17, 18, 20, 26, 27, 29), based on either creatinine levels or urine output. The definition of ARF varied considerably between the studies. The creatinine level for defining ARF in one study (9) was more than 120 mmol/l, whereas in another study (8) it was as high as more than 500 mmol/l. Oliguria was taken as evidence for ARF in two studies (11, 26).

Six studies (4, 5, 6, 12, 19, 22) dealt exclusively with ARF requiring renal replacement therapy.

Only 11 papers (1, 4, 5, 8, 10, 18, 19, 23, 24, 26, 29) mention the duration of follow-up. The duration of follow-up in these studies ranged from 60 days in one study (18) to a mean of 13 years (range 10-19.8 years) in another study (24). The maximum follow-up period in the studies with adult patients is 90 days and for children it is 19.8 years.

Results of studies in the adult population

ARF treated in non-ICU settings

The proportion of patients developing ERF after ARF has been variously reported as 1% (17), 2% (13), 2.7% (22), 4.5% (1), 8% (9), 10% (2), 12% (3), and 16.7% (5). In one study (11) reporting the outcome of ARF due to crush injuries following an earthquake, all the surviving patients were discharged with normal renal function. Hence in this study the proportion of patients developing ERF is 0%.

ARF treated in an ICU setting

The incidence of ERF in patients treated for ARF in an ICU setting varies considerably. The percentage of patients treated in an ICU who develop ERF following ARF has been reported variously as 7% (18), 8.3% (22), 17.9% (12), 33% (5), 34.3% (7) and 40% (27).

One study (28) assessed ICU patients with ARF due to ACE inhibitors in 64 patients, 21 of whom had pre-existing CRF not requiring RRT. Nine patients required dialysis during the acute phase. Only 2 patients with pre-existing CRF went on to regular HD 3 years after the ARF episode; however as their creatinine had returned to baseline following discharge, it is unlikely that the ARF worsened progression of their ARF. One study (21) showed that whilst only 1.6% of survivors of ARF with previously normal renal function developed ERF, this proportion was 33% in patients with pre-existing CRF.

Results from population based studies

Again, there is a huge variation in the proportion of patients developing ERF based on data from four prospective population based studies. This proportion varies from 2% (13) to 26% (19). The other two studies (4, 8) give figures of 20% and 25% respectively.

Results of studies in the paediatric population

The outcome of paediatric cases of Haemolytic Uraemic Syndrome (HUS) was dealt with in five studies (10, 14, 23, 24, 26). The proportion of patients with ARF due to HUS developing ERF was variously 1% (23), 3% (24), 3.2% (10), 5% (14), 5% (23) and 7% (26). In the two studies assessing outcomes in children with ARF due to any cause, the proportion developing ARF has been reported to be 2.2% (29) and 6% (16).

Conclusion

The above discussion indicates that the proportion of patients developing ERF varied widely according to different studies. According to one review of literature, the proportion of survivors of ARF developing ERF ranged from 0-71% (15). The wide variation may be due to the different populations assessed in the studies (children vs adults, patients in ICUs vs those in general wards), different underlying problems causing ARF and different definitions of ARF. The follow-up periods also vary widely between the studies, and therefore it is possible that shorter-term studies may not have allowed sufficient time for the patients to have progressed to ERF, thereby giving falsely low percentages. The search for the reasons for the wide variation in the development of ERF following ARF, such as age, underlying disease process and comorbid factors, will be explored for Question 23, which deals with factors associated with failure to recover renal function.

Summary statements

- Definition of ARF varies widely according to the study.
- The proportion of patients developing ERF after ARF in the adult population ranges from 1% (17) to 34.3% (7); one study (11) reported that none of the survivors of ARF due to crush injury following an earthquake developed ERF.
- According to studies in the adult population that mentioned follow-up, the duration of follow-up ranged from 60 days to 90 days.
- The proportion of patients developing ERF after ARF in children ranges from 1% (23) to 7% (26).
- According to studies in the paediatric population that mentioned follow-up, the duration of follow-up ranged from one year to 19.8 years.
- Exploration of the reasons for the variations in the proportion of patients developing ERF after ARF will help identify factors associated with non-recovery of renal function following ARF, and this will be dealt with in Question 23.

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Question 23

What factors are associated with failure to recover renal function (eg cause of ARF, age)?

Comments on the evidence

While examining the publications for some of the other questions, it became clear that they also addressed this one. Thus, the relevant papers were included that were retrieved for all of the other questions regarding epidemiology, early identification of patients with pre-existing CKD and acute deterioration of previously normal renal function, follow-up, and factors associated with non-renal recovery of renal function (questions 11, 12, 21, and 23).

Whilst several studies have dealt in great detail with prognostic factors for patients' survival, very few papers have information regarding factors influencing recovery of renal function following ARF.

A total of 15 papers that were relevant to this question were found. Six were from Europe (2, 3, 4, 6, 7, 1), four were from the USA (5, 8, 9, 14), three were from the UK (1, 10, 13), one from Argentina (11) and one from Japan (15).

In children with haemolytic-uraemic syndrome (HUS), failure to recover renal function is associated with non-diarrhoea associated HUS (12), dialysis duration (12, 10), oliguria more than 14 days (12), anuria ranging from more than 7 days (3) to more than 11 days (11), hypertension (3), reduced effective plasma renal flow two years after onset of ARF (3) and renal biopsy finding of arterial thrombotic microangiopathy (6).

One study (4) found that GFR estimated by renal 131I-ortodohippurate clearance levels at seven days post-ARF onset was associated with failure to recover renal function, if it was less than 150 mls/min. Another study (5) found that patients who had high initial uptake of MAG3 isotope in the liver compared to the kidneys on scintigraphy, had poor recovery of renal function.

Failure to recover renal function in adults following ARF has been associated with advanced age (8). Aetiology of renal failure may have a bearing on renal recovery. Elderly patients with medical causes of ARF have a worse renal outcome when compared to those with renal failure due to trauma or surgical causes (14). One study (1) has found that, in patients with ARF due to multiple myeloma and renal parenchymal causes such as rapidly progressing glomerulonephritis (RPGN), the renal outcome is worse when compared with other ARF causes such as obstruction or renovascular disease. Oliguria has been found in some studies to be associated with failure to recover renal function (7, 9, 16). High APACHE III scores (9), mechanical ventilation (16) and use of diuretics (9) during the ARF episode have been found to be associated with failure to recover renal function in patients in an ICU setting. In patients with ARF due to obstetric causes, acute cortical necrosis was a poor prognostic factor (Turney 1989). One study (2) dealing exclusively with elderly patients with ARF did not find any correlation between oliguria, need for dialysis, mean serum creatinine concentration and renal function recovery.

Summary statements

- In children with HUS, failure to recover renal function is associated with non-diarrhoea associated form of HUS (Tonshoff 1994), duration of anuria and dialysis (12, 3), hypertension (3), and renal biopsy finding of arterial thrombotic microangiopathy. (Level 3) (6)
- In adults, advanced age (8), aetiologies of ARF such as multiple myeloma and RPGN (1), and oliguria (7, 9) were risk factors for failure to recover renal function. (Level 3)

- In patients in an ICU setting, high APCHE III scores (9), mechanical ventilation (15) and use of diuretics (9) have been associated with failure to recover renal function. (Level 3)
- In ARF due to obstetric causes, acute cortical necrosis was a poor prognostic factor for renal function recovery (13). (Level 3)

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Evidence concerning the cost-effectiveness of Angiotensin-converting enzyme inhibition in treating chronic kidney disease.

The following studies relating to the cost-effectiveness of ACE inhibitors in the treatment of people with CKD were identified and considered by economic analysts in the Department of Health, in the course of work on the NSF for Renal Services:

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2. Garattini L, Brunetti M, Salvioni F, Barosi M. Economic evaluation of ACE inhibitor treatment of nephropathy in patients with insulin-dependent diabetes mellitus in Italy. PharmacoEconomics 1997; 12(1): 67-75

3. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. New England Journal of Medicine 1993; 329(20): 1456-62

4. Clark WF, Churchill DN, Forwell L, madconald G, Foster S. To pay or not to pay? A decision and cost-utility analysis of angiotensin-converting-enzyme inhibitor therapy for diabetic nephropathy. Canadian Medical Association Journal 2000; 162(2): 195-98

5. Ruggenenti P, Pagano E, Tammuzzo L, Benini R, Garattini L, Remuzzi G. Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. Kidney International 2001; 59(1): 286-94

6. Rodby, RA, Firth, LM, Lewis EJ. An economic analysis of captopril in the treatment of diabetic nephropathy. Diabetes Care 1996; 19(10): 1051-61.

7. Trivedi HS, Pang MMH, Campbell A, Saab P. Slowing the progression of chronic renal failure: economic benefits and patients' perspectives. American Journal of Kidney Disease 2002; 39: 721-29

END OF LIFE CARE

The markers of good practice for Quality requirement four, on End of life care, are all supported by Level 4 evidence – ie, 'Expert opinion, including the views and experiences of people with renal failure and their carers'. During development of this module of the NSF meetings were held with patients, carers and families, with members of the multidisciplinary team, and with representatives of faith groups.

RESEARCH IN PROGRESS OR RECENTLY COMPLETED, FUNDED BY THE DEPARTMENT OF HEALTH

Health Technology Assessment Programme (HTA)

A policy for the drug treatment of high blood pressure. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy; M Law, N Wald, J Morris. (HTA ref: 93/05/01 – published 2003, Vol 7, No 31)

Systematic review of urine albumin testing for early detection of diabetic complications; D Newman. (HTA ref: 96/33/02 – published 2005, Vol 9, No 30)

A systematic review of tests for the diagnosis and evaluation of urinary tract infection in children under five years; J Kleijnen. (HTA ref: 01/66/01 – publication expected Summer 2006)

Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation; J Bryant, C Cave, B Mihaylova, D Chase, L McIntyre, K Gerard et al. (HTA ref: 00/21/01 - published 2002, Vol 6, No 18)

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

AREAS FOR FURTHER RESEARCH

In compiling this report, the Evidential team identified topics where further research would be helpful. These include the Research Topics below.

A need has been identified by those dealing with children and young people with kidney disease for more research studies with long-term follow-up, providing information on long-term outcomes.

Research Topics

1. The consequences of the age-related decline in GFR in older adults.

2. The effects of using ACE inhibitors to prevent CKD specifically, over and above cardiovascular disease.

3. The long-term effects, if any, of the correction of renal anaemia in stages 1, 2 and 3 CKD; in particular, whether it delays development or progression of complications such as cardiovascular disease.

4. Studies in the USA show 30% of the close relatives of people on dialysis have CKD. What is the equivalent figure for the UK population?

5. What follow-up is appropriate following an episode of ARF, for patients whose renal function was normal before it, and who recover normal renal function afterwards.

6. How the palliative care needs of people with renal failure can best be met: generic and renal-specific aspects of care.