SUPPLEMENTARY INFORMATION for "Outcomes of early versus late nephrology referral in chronic kidney disease – a systematic review."

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Outcomes of early versus late nephrology referral in chronic kidney disease – a systematic review

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Both authors do not have any conflict of interest to declare. Both authors had equal access to data and contributed equally to the work and manuscript. The authors did not have any financial arrangements, any relationship with people or organisations that could bias the submitted work. The authors had full access to the data reviewed, and took the final responsibility to submit the work. The first author, Neil Smart, was funded by the Commonwealth Government of Australia’s Department of Health and Aging Primary Healthcare Research Evaluation and Development program (2006-09) during the time he undertook the work, with no influence on the study design, data collection, analysis, interpretation or on the decision to submit.

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Abstract

Background As late provision of specialist care, prior to starting dialysis therapy, is believed to be associated with increased morbidity and mortality, a systematic review was undertaken to evaluate clinical outcomes relating to early versus late referral of patients to nephrology services.

Methods: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE were searched up until September 2008 for studies of early versus late nephrology referral in adult (>18 years) patients with chronic kidney disease. Early referral was defined by the time period, at which patients were referred to a nephrologist.

Findings: No randomized, controlled trials were found. Twenty seven longitudinal cohort studies were included in the final review, providing data on 17,646 participants; 11,734 were referred early and 5,912 (33%) referred late. Comparative mortality was higher in patients referred to a specialist late versus those referred early. Odds ratios (OR) for mortality reductions in patients referred early were evident at 3 months [OR 0.51 (95% CI 0.44-0.59) p < 0.00001] and remained at five years [OR 0.45 (95% CI 0.38-0.53)] both p < 0.00001. Initial hospitalization was 8.8 days shorter with early referral (95% CI -10.7 to -7.0 days, p < 0.00001). Differences in mortality and hospitalization data between the two groups were not explained by differences in prevalence of diabetes mellitus, previous coronary artery disease, blood pressure control, serum phosphate, and serum albumin. However, early referral was associated with better preparation and placement of dialysis access.

Interpretation: Our analyses show reduced mortality and hospitalization, better uptake of peritoneal dialysis and earlier placement of arterio-venous fistula for haemodialysis with early nephrology referral.
BACKGROUND

Chronic kidney disease (CKD) is a complex illness, with significant impact on an individual's quality of life, longevity, use of medical resources and public health expenditure. A systematic review[1] of multiple observational studies up to 2005 reported increased mortality and hospitalisation in those patients referred late to specialist renal services. The aim of this study was to conduct a broader systematic review, examining whether early versus late referral of adult chronic kidney disease patients to nephrology services also impacted on choice of dialysis modality, placement of relevant dialysis access and other measures such as serum biochemistry.

METHODS

A systematic review protocol (CD007333) was written and published in Issue 3, 2009 of the Cochrane Renal group [2]. A systematic search was conducted to identify published studies of outcomes in patients with chronic kidney disease, receiving dialysis, including timing of referral to nephrology services. Key search terms are listed below, no limits were used. The following databases were searched (search dates included); MEDLINE (1966 to September 2008), The Cochrane Renal Groups specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, EMBASE (1980 to September 2008). The MEDLINE search strategy can be seen in Table 1.

Types of participants

Inclusion criteria

Studies of adult chronic kidney disease patients referred for evaluation by a nephrology service, where the outcome data are presented as two distinct groups,
early and late referral, were included. Early and late referral were defined in terms of the time period between specialist nephrology referral and commencing dialysis. There were no language restrictions.

**Exclusion criteria**

Studies involving participants with acute renal failure or children (<18 years) or those using eGFR for defining early and late referral were excluded.

**Types of interventions**

The intervention was specialist nephrology care versus standard care.

**Types of outcome measures**

1. Timing of referral to specialist in relation to subsequent dialysis initiation.
2. All-cause mortality, hospitalisation (only initial hospitalisation was recorded, several authors were contacted for clarification).
3. Measure of renal function as indicated by serum creatinine
4. Systolic and diastolic blood pressure.
5. Biochemical parameters: serum calcium and phosphate, haemoglobin, lipid profile, serum albumin
6. Use of erythropoietin.
7. Prevalence of other co-morbid disease e.g. diabetes, cardiovascular disease, heart failure, stroke, chronic obstructive pulmonary disease.
Types of Studies

The review was based on prospective and retrospective cohort studies, as our search did not yield a single randomised controlled trial or quasi-randomised controlled trial, and the next best level of evidence being longitudinal cohort studies.

Data extraction and management

The titles and abstracts were screened independently by two review authors (NS, TT) who assessed retrieved abstracts and, if necessary full texts of those studies which satisfied the inclusion criteria. Inclusion or exclusion disputes were resolved by an independent colleague. A supporting PRISMA statement summarizes reasons for excluding and including studies. Data extraction was archived to standardized data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one trial existed, reports were grouped together and the most recent or most complete data set were used. Any discrepancies between published versions were highlighted. Any further information required from the original trial author was requested by written correspondence and any relevant information obtained was archived.

For discrete data, results were expressed as odds ratio (OR) with 95% confidence intervals (CI). In two studies mortality data was available for 3 months, 12 months and 5 years [3, 4], we calculated percentage mortality rates for these data collection periods. This was done by calculating the number of deaths in each group, for each time period and dividing by the total number of patients in each group. The mean difference (MD) was used where continuous scales of measurement were used to
assess the effects of treatment (E.g. serum creatinine). Data was pooled and analysed using the fixed-effects model to ensure robustness of the chosen model and susceptibility to outliers. Where appropriate, we calculated the number needed to treat, for dichotomous events such as mortality and hospitalization using the inverse of absolute risk reduction. Sub-analyses were conducted, removing studies that used a period less than 3 months or more than 4 more to define early referral, these analyses were not pre-specified.

Assessment of heterogeneity

Heterogeneity was analysed using a $\chi^2$ test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the $I^2$ test [5]. $I^2$ values of 25%, 50% and 75% corresponded to low, medium and high levels of heterogeneity respectively.

RESULTS

Our search identified 114 studies, 9 duplicate studies were removed, 14 were excluded based upon title or abstract. Full manuscripts of 91 papers were obtained and data was extracted from 27 studies, of the other 64 studies, 30 did not have relevant outcome measures, 19 were review articles, 6 were studies of acute renal failure, 5 were paediatric studies and 4 did not meet our definition of early referral (see figure 1). The 27 included studies had 17,646 participants; 11,734 were referred early and 5,912 referred late. The mean number of early and late referred participants was 451±720 and 227±313 per study respectively. Approximately one third (33.5%) of participants were referred late. The period defining early referral varied between 1 and 6 months, with the most popular definition of early referral being 3 months, in 13 studies. Only 4 studies were prospective cohort studies, the remainder were
retrospective cohort studies (21) or database analyses (2). Supplementary electronic table lists characteristics of the original 27 studies.

**Mortality**

Patients who were referred earlier showed a cumulative mortality benefit at 3, 6, 12 months and 5 years compared to those referred late. Patients referred early showed reduction in mortality at 3 months (Figure 2a), 6 months (only 1 study, no figure), 12 months (Figure 2b) and 5 years (Figure 2c) respectively. Sub-analyses were conducted by removing studies that had a definition of early referral other than 3-4 months prior to starting RRT. Sub-analyses conducted on 3 month, 12 month and 5 year mortality data showed similar magnitude of reductions and statistical significance (all p<.00001). Analysis of the two studies providing 3 month, 12 month and 5 year mortality data showed reduced mortality for patients referred early. The mortality reduction was evident at 3 months and remained for 60 months (Figure 3).

**Duration of initial hospitalization**

Duration of hospitalisation was reported in six studies and meta-analysis showed shorter hospitalisation period mean difference -8.8 days, (95% CI -10.7 to -7.0 days, p <0.00001) in those referred earlier to a nephrologist (figure 4). Sub-analysis of those studies defining early referral between 3-4 months, showed similar hospitalization data mean difference -7.7 days, (95% CI -14.6 to -0.9 days, p = 0.03), showed similar magnitude of reduction.

**Peritoneal Dialysis (PD)**
Meta-analysis of 14 studies showed peritoneal dialysis (PD) uptake was more common in those patients referred earlier to a nephrologist OR 2.1 (95% CI 1.9 to 2.3, p < 0.00001) (figure 5).

**Temporary Access**

Eleven studies reported the number of patients who had temporary vascular access on commencement of dialysis. Patients referred earlier to a nephrologist were less likely to have temporary vascular access at the start of dialysis OR 0.18 (95% CI 0.16 to 0.20, p<0.00001) (figure 6a).

**Permanent Access**

Meta-analysis of 7 studies showed placement of permanent vascular access, namely in the form of arterio-venous fistulae, to be more common in earlier referred patients OR 3.0 (95% CI 2.5 to 3.5, p < 0.00001) (Figure 6b).

**Haemoglobin (Hb)**

In the 12 studies that reported plasma Hb levels, meta-analysis showed higher levels mean difference 11.1 g·L⁻¹ (95% CI 10.3 to 12g·L⁻¹, p < 0.00001) in patients referred to nephrology specialist services earlier (Electronic supplementary Figure 7).

**Use of Erythropoietin (EPO)**

Meta-analysis of seven studies showed that erythropoietin usage was more common in patients referred early to nephrology care OR 3.9 (95% CI 3.2 to 4.9, p< 0.00001) (Electronic supplementary Figure 8).

**Serum Creatinine**

Eleven studies reported serum creatinine levels. Meta-analysis found lower levels at the start of dialysis in those patients referred to specialist care earlier mean difference
-93 micromol/l, (95% CI -112 to -73, micromol/l, p < 0.00001) (Electronic supplementary Figure 9).

**Other outcome measures**

There were no differences between early and late referred patients in gender distribution, nor in the prevalence of coronary artery disease, diabetes mellitus, chronic obstructive airways disease, systolic and diastolic blood pressures. However prevalence of cerebrovascular disease OR 0.85 (95% CI 0.73-1.00, p=0.05), inability to ambulate OR 0.63 (95% CI 0.47-0.85, p=0.002) were significantly lower in early referrals. Prevalence of congestive heart failure (OR 1.23 (95% CI 1.10-1.39, p=0.0005) was higher in the early referred group. Serum phosphate, albumin, lipids and estimated glomerular filtration rate (eGFR) were not significantly different between the two groups, although serum calcium showed a mean difference of 0.03 micromol/l, being higher in those referred early (95% CI 0.01-0.05 micromol/l, p=0.0009). It was not possible to pool the data from the two studies that measured quality of life issues as different measurement scales were used.

**Number Needed to Treat**

We calculated that the number of patients needed to be referred earlier to prevent one death at 12 months was ten, at 3 months the number needed to treat was also 10, at five years the number need to treat was 5.

**Discussion**

Our meta-analysis showed that patients referred earlier to nephrology services had reduced mortality and hospitalization. The benefits seen in the earlier referred patients appear to be acquired independently of differences in traditional cardiovascular risk
factors such as prior coronary artery disease, diabetes mellitus, systolic and diastolic blood pressures, lipid profile and renal biochemistry. It appears that better fistula preparation and placement of dialysis access may explain improved prognosis in earlier referred patients with chronic kidney disease.

**Mortality**

Our analyses showed the mortality reduction for patients referred early were 49%, 41%, 45% and 55% at 3, 6, 12 months and 5 years respectively. To highlight possible effects of excessive mortality from one time period, we serially removed mortality data at 3 months and then at one year from the 5 year mortality data for each of the two studies where the data were available [3, 4] and calculated the percentage mortality rates. The reduction in mortality for patients referred early was evident at 3 months and remained for 60 months, although lower mortality rates were most noticeable at 0-3 months (figure 5). After three months, mortality rates ran in parallel, suggesting that the mortality difference between groups noted at 5 years could be related to the initial 0-3 month mortality, although we acknowledge this approach may be flawed unless person years at risk (primary data unavailable) are similar. The meta-analysis by Chan et al [1], reported a time-to-event analysis and a 12 month mortality sub-analysis, supporting a clear mortality reduction for patients referred earlier to a nephrologist.

**Hospitalization**

To clarify the definition of hospitalization for this analysis we chose to include those studies reporting initial hospitalization and not total hospitalization. Our analysis, like that of Chan [1] showed a respective reduction of 9 and 12 days for those referred
early. Earlier referred patients are possibly better prepared for dialysis initiation, resulting in fewer complications and emergency admissions.

**Peritoneal Dialysis**

Our analysis showed that patients referred earlier had twice the uptake of peritoneal dialysis (OR 2.1). Multivariate analysis has previously shown that appropriate patient education is the best predictor of peritoneal dialysis uptake [6], a modality which has been reported to provide better quality of life, more satisfaction with overall care and less intrusion on their lives compared to hemodialysis [7]. It is possible that the earlier referral facilitated better patient education.

**Vascular access for hemodialysis**

Our analysis showed the likelihood of early referred patients receiving temporary vascular access was significantly reduced. Previous work has shown that reduced temporary vascular access is associated with improved mortality and morbidity through reduced systemic infection rates [8, 9], and avoiding issues relating to emergency dialysis such as pulmonary oedema and severe uremia [9].

Placement of an arterio-venous fistula requires investment of sufficient time in patient education and assessment as well as providing patient choice. Practical experience shows that typically 4 months surveillance and intervention is often required before a fistula is ready for dialysis and this may explain the convention of defining late referral as less than 3-4 months of nephrology care, as demonstrated in 13 of the studies reviewed.

**Haemoglobin and Erythropoietin use:**

Our review identified early referral to be associated with better haemoglobin levels, which could translate to better quality of life, reduction in left ventricular hypertrophy as well as better physical and cognitive functioning [10]. Early referral was also
associated with increased use of erythropoietin and it could be inferred that improved anaemia management is achieved by specialist nephrology teams.

**Other outcome measures:**

Our analysis showed patients referred early to nephrology services to have a lower mean serum creatinine of 93 micromol/l. The lower creatinine levels at dialysis initiation may have contributed to the reduced mortality noted, via lead time bias, as patients may start dialysis at an earlier stage of the disease. However, evidence has emerged via the IDEAL trial[11] that initiation of dialysis at a lower serum creatinine does not improve survival.

Our data suggests that prevalence of co-morbid illness’ did not differ between the early and late referral groups. However, the available data did not allow an analysis of severity of co-morbid illness’. Our data also suggest historically, about a third of patients have been referred late to a nephrologist, these data correspond to recent survey data from the UK [12]. One explanation for sub-optimal timing of nephrology referral is the limited capacity of tertiary care systems to manage the required patient volume [13]. Recent work has suggested that chronic kidney disease guideline implementation results in significant increases in nephrology referral and additional investigation which are associated with additional costs. It has been suggested that these costs could be recouped by delaying dialysis requirement by 1 year in one individual per 10,000 patients managed based on current UK guidelines [14]. To put this into context, in Australia, in 2007, haemodialysis was more expensive than peritoneal dialysis, AUS$ 82,764 versus AUS$ 56,828 per patient/year [15].

**Limitations**

Cohort study data presents the risk of drawing causal inferences that may be confounded observations, however, for this study, it is the best level of evidence that
is likely to be available. Differences in study sizes, treatment and referral practices in different countries at different time periods may account for heterogeneity between studies. In order to evaluate publication bias, funnel plots were conducted that did not reveal publication bias. Thirteen of twenty seven studies used 3 months as the definition of early referral, the definition varied between 1 and 6 months. Some of the benefits accrued by early referred patients are likely to be due to lead time bias, as discussed earlier. Despite these limitations meta-analysis was justified, as ethical and resource limitations are likely to preclude a randomized, controlled trial.

**Conclusions**

Patients referred earlier to a nephrologist demonstrate significantly reduced short- and long-term mortality, hospitalization, anaemia as well as better dialysis preparation. Our data suggest blood pressure, serum phosphate and serum albumin appear to be managed equally by specialist and non-specialist physicians. Neither did our analysis find any differences in the prevalence of co-morbid illness’ often reported with late referral. Our analyses suggest that reduced mortality and hospitalization are perhaps a result of better preparation and placement of dialysis access associated with early specialist referral.

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**Clinical significance:**
• Early referral is also associated with reduced mortality and hospitalisation and patients had better dialysis preparation.
• Both nephrologists and non-nephrology physicians managed blood pressure, lipid profile, and early complications of chronic kidney disease equally well.
• The improvement in mortality and hospitalisation rates may be related to better dialysis preparation including early placement of dialysis access.

References:


