

Early referral of patients with pre-end-stage kidney disease

Date written: September 2005

Final submission: September 2006

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GUIDELINES

Patients at high risk of progressive deterioration in kidney function should be referred to a nephrology service for specialist management of renal failure (Level II evidence, one randomized controlled trial (RCT)).

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

There have been a large number of observational studies examining the role of early referral in the progression of chronic kidney disease (CKD) to end-stage kidney disease (ESKD). Most of these data are heavily confounded by the characteristics of the patients that are referred late compared with those who present early, making the precise role of referral difficult to accurately interpret.

- The Modification of Diet in Renal Disease study group¹ prospectively examined the rate of decline of renal function in patients with CKD excluding patients with insulin-dependent diabetes. Although this study was not designed to test the effect of early referral on progression, patients with an initial glomerular filtration rate (GFR) between 25 and 55 mL/min per 1.73 m² had an average annual rate of decline of residual renal function of between 3 and 13 mL/min per year. In a subgroup of 255 patients with poorer initial GFR of 13–24 mL/min per 1.73 m² (i.e. later referral), the annual average rate of decline of renal function was not significantly different, varying between 2 and 8 mL/min per year.

- Ellis *et al.*² reported a retrospective review of 198 patients accepted for renal replacement therapy at Kings College, London over a 2 year period from 1 January 1996 to 31 December 1997. In the late referral group (<12 weeks before commencing renal replacement therapy, n = 64), there was objective evidence of kidney disease for at least 8 weeks in 50% of patients and 22% of patients had evidence of renal disease for at least 1 year before the time of referral. Sub-optimal management of CKD before referral to the nephrology service was common. Only 33% of diabetic patients were treated with an angiotensin converting enzyme (ACE) inhibitor and 49% of patients with CKD and hypertension had inadequate control of blood pressure at the time of referral to the nephrology service.

- Lhotta *et al.*³ studied 75 patients with CKF, stratified into early (>20 mL/min per 1.73 m², n = 33) and late (<20 mL/min per 1.73 m², n = 42) referral groups. While comorbid complications and age were strongly associated with mortality, and late referred patients were more likely to be older and have comorbid disease, the independent effect of late referral was comparatively minor.

- Caravaca *et al.*⁴ examined the determinants of the rate of decline of renal function in 230 patients with pre-ESKD. Overall, the level of proteinuria and haemoglobin (Hb) at referral and the presence of diabetes mellitus were the strongest determinants of adverse outcomes. Although late referral was not independently associated with progression in this study, it could be argued that earlier referral may offer the ability to reduce both proteinuria and anaemia.

- John *et al.*⁵ identified unreferral patients with renal impairment from an established database and followed them up to establish survival, rate of referral and change in GFR. Overall, most unreferral patients had stable (impaired) renal function, though some (few) patients progressed. Clearly identifying those patients at greatest risk of progressive renal disease is a key to optimize referral strategies.

Early referral of patients with CKD specifically to a nephrologist, may also slow the progression of kidney disease.

- In a retrospective review of patients commencing dialysis in a metropolitan New York hospital, Ifudu *et al.*⁶ reviewed the outcomes of 139 patients who had been commenced on dialysis between 1990 and 1994, stratified according to whether they had received pre-dialysis care from a nephrologist (43% of cohort), non-nephrologist physician (45%) or who had received no pre-dialysis medical care (12%). Patients who had a period of pre-dialysis care by a nephrologist had a significantly reduced rate of decline in serum creatinine concentration.

What constitutes early referral?

Clinical studies have used many different definitions of what constitutes 'an early referral'. For adequate preparation and planning for renal replacement therapy,

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patients need about 18 months before anticipated dialysis initiation in order to minimize the risk of future adverse outcomes.

Who to refer to a nephrologist?

Patients at high risk of progressive deterioration in kidney function should be referred to a nephrology service for specialist management of renal failure. These patients include:

- Patients with GFR < 30 mL/min per 1.73 m² (Level III–IV evidence). However, some have suggested that intervention even at 30 mL/min per 1.73 m² is too late with the prior development of bone disease and other complications of uraemia.
- Patients with CKD and a GFR > 30 mL/min per 1.73 m² and rapidly declining kidney function or clinical features to suggest that renal function may decline more rapidly such as:
 - marked or uncontrolled hypertension
 - proteinuria (>1 g/24 h)
 - significant comorbid illness
 - anaemia (<110 g/L).

BACKGROUND

Many patients with potentially serious yet possibly reversible kidney disease are not referred until substantial irreversible scarring has occurred. Indeed, recent surveys suggest that over 30% of patients with CKD are referred later than ideal. Late referral of patients with kidney failure is associated with increased patient morbidity and mortality, increased need for and duration of hospital admission and increased initial costs of care following the commencement of dialysis. More frequent pre-ESKD care confers increased survival benefit. Additional benefits include identifying and treating reversible causes of renal impairment and managing the multiple coexisting conditions associated with chronic renal disease. Referral time affects the modalities of the treatment. Clinical outcomes can be improved by referring patients with CKD to a nephrology service well in advance of the need for dialysis.^{7,8} These issues have been discussed elsewhere in the CARI guidelines (Acceptance onto dialysis: Timing of referral of chronic renal failure patients to nephrology services). The objective of this specific guideline was to evaluate the available clinical evidence pertaining to the impact of early referral in preventing progressive renal impairment, and ultimately delaying time to ESKD.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for CKD were combined with MeSH terms and text words for early referral and consultation. The search was carried out in Medline (1966 to November Week 2, 2004).

Date of search: 11 November 2004.

WHAT IS THE EVIDENCE?

While there have been a number of observational studies and audits that have documented the increased morbidity of late referred patients, there is comparatively little data on the effect of early referral on the progression to kidney failure. Clearly, this is a difficult question to answer, as the rate of progression in early disease in patients referred late is uncertain.

There has been one RCT that formally tests this hypothesis:

- Binik *et al.*⁹ in a randomized study of 204 patients showed that early multidisciplinary interventions delayed the onset of ESKD. These interventions consisted of a specially prepared slide-lecture show concerning kidney diseases and their treatment that was delivered by a trained research assistant.

SUMMARY OF THE EVIDENCE

Given the utility of early referral in improving other outcomes, this question is largely academic. In addition, each of the interventions to slow progressive kidney disease detailed in these guidelines are more efficacious the earlier they are initiated. Indeed, a number of RCTs detailed in these guidelines have shown that treatment in patients with established renal impairment is less effective in preventing ESKD than interventions instituted at the disease onset or at diagnosis.

The specific utility of any cut-point to define referral has not been tested in Level I or II trial, so categorical guidelines cannot be stipulated. Nonetheless, for adequate preparation and planning for renal replacement therapy, patients need about 18 months before anticipated dialysis initiation in order to minimize the risk of future adverse outcomes.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association 2006:¹⁰

Referrals should be made as follows:

Immediate:

- Suspected acute kidney failure
- ARF superimposed on CKD
- Newly detected ESKD (GFR < 15 mL/min per 1.73 m²)
- Accelerated or malignant phase hypertension with suspicion of underlying kidney disease (or if there is no specialist hypertension service available locally)
- Hyperkalaemia, serum potassium >7.0 mmol/L

Urgent outpatient:

- Nephrotic syndrome
- Newly detected stage 4 (unless known to be stable) or stable stage 5 CKD
- Multisystem disease (e.g. systemic lupus erythematosus (SLE), systemic vasculitis) with evidence of kidney disease
- Hyperkalaemia, serum potassium 6.0–7.0 mmol/L (after exclusion of artefactual and treatable causes)

Routine outpatient:

- Refractory hypertension (defined as sustained BP > 150/90 mmHg despite combination therapy with three drugs from complementary classes)
- Acute deterioration in kidney function (defined as a fall of GFR of >15% or rise of serum creatinine concentration of >20% from baseline) associated with the use of ACE inhibitor or angiotensin receptor blocker (ARB)
- Proteinuria (urine protein > 100 mg/mmol) without nephrotic syndrome
- Proteinuria with haematuria
- Diabetes with increasing proteinuria but without diabetic retinopathy
- Stage 3 CKD with haematuria
- Urologically unexplained macroscopic haematuria (with or without proteinuria)
- Recurrent unexplained pulmonary oedema with clinical suspicion of renal artery stenosis
- Falling GFR (>15% fall over 12 months) with clinical suspicion of ARAS
- PTH > 70 ng/L (7.7 pmol/L) after exclusion or treatment of vitamin D deficiency
- Stable stage 4 CKD if referred

Canadian Society of Nephrology:¹¹ Earlier referral to nephrologists of patients with elevated creatinine levels is expected to lead to better health-care outcomes and lower costs for both the patients and the health-care system. Refer patients with a creatinine clearance of <30 mL/min to a nephrologist for opinion regarding management of renal failure. All patients with newly discovered renal insufficiency (as evidenced by serum creatinine elevated to a level above the upper limit of the normal range of that laboratory, adjusted for age and height in children) must undergo investigations to determine the potential reversibility of disease, to evaluate the prognosis and to optimize planning of care. All patients with an established, progressive increase in serum creatinine level should be followed with a nephrologist.

European Best Practice Guidelines: No recommendation.

INTERNATIONAL GUIDELINES

NIH Consensus Conference on Morbidity and Mortality Associated with Dialysis:¹² Pre-dialysis referral to a renal team, consisting of a nephrologist, dietitian, nurse, social worker and mental health professional, allows time to establish a working relationship, to acquaint the patient with the various modes of renal replacement therapy, and to provide information on dialysis access, nutritional modification, avoidance of potentially nephrotoxic drugs and potential financial support for services. It is essential to initiate the medical interventions discussed below, to reduce mortality and morbidity as soon as possible. Referral of a patient to a renal team should occur when the serum creatinine has increased to 1.5 mg/dL in women and 2.0 mg/dL in men.

IMPLEMENTATION AND AUDIT

Data on the initial GFR at which patients are referred and the time at which patients were referred relative to the commencement of dialysis should continue to be obtained through the ANZDATA registry.

Goal objective: more than 80% of patients commencing dialysis should be referred early, in accordance with the above guideline and should receive appropriate pre-dialysis management under the supervision of a nephrologist.

SUGGESTIONS FOR FUTURE RESEARCH

Timing of referral of CKF patients should be recorded as part of ANZDATA.

CONFLICT OF INTEREST

Merlin Thomas has a Level II b conflict of interest according to the conflict of interest statement set down by CARI.

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