Chronic kidney disease

Part 2: complications and end-stage renal disease

Patients with chronic kidney disease likely to need dialysis in the future should be referred early to renal physicians for review and education about dialysis options and possible transplantation.

MAUREEN LONERGAN
BMedSc, MB BS, FRACP, PhD

Dr Lonergan is a Clinical Professor at the University of Wollongong, Wollongong, and Director of Renal Medicine for the Southern Sector of the South Eastern Sydney and Illawarra Area Health Service, NSW.

The current 6% annual growth in the number of people requiring dialysis will have a profound effect upon an already strained health system. However, early identification of people with kidney disease and aggressive intervention can slow the loss of renal function and also reduce the risk of cardiovascular disease, thus lessening the healthcare burden.

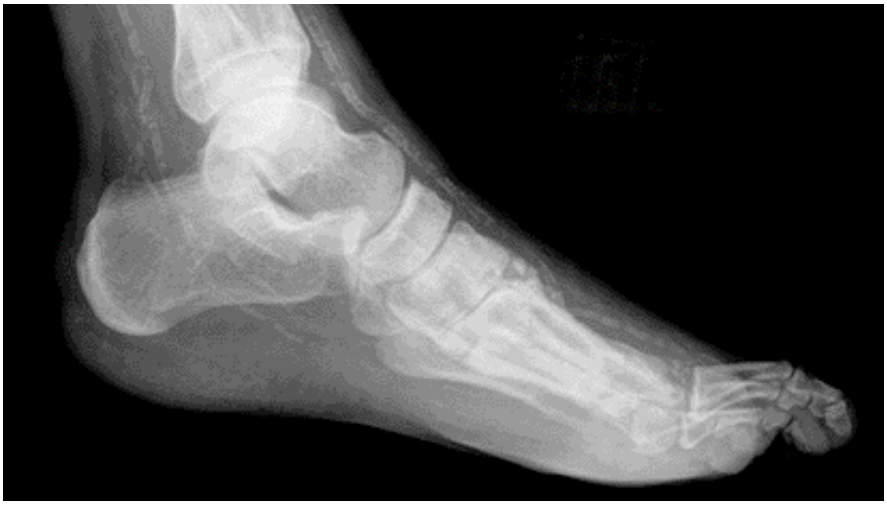
This article, the second of two on chronic kidney disease (CKD) by this author, covers the management of the complications that can arise as renal function is progressively lost and the issues and decisions that need to be made concerning dialysis or transplantation. The detection of patients with renal disease and the management of these patients to preserve their renal function were discussed in the first article, which was published in the February 2008 issue of *Medicine Today*. The two articles provide a common sense approach to the patient with chronic renal failure but do not seek to explore existing controversies in the management of chronic renal failure.

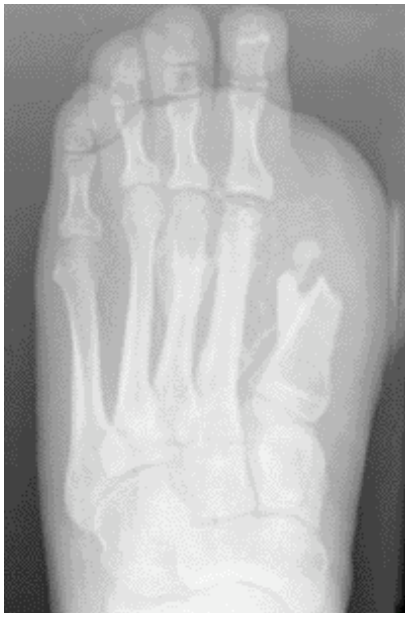
Management of complications

The kidneys have many roles in maintaining homeostasis. These relate not just to fluid and electrolyte balances but also to bones, anaemia and nutrition. The risk of developing complications increases progressively as renal function decreases.

IN SUMMARY

- **The complications of chronic kidney disease include metabolic acidosis, hyperkalaemia, vitamin D deficiency, hyperparathyroidism and anaemia, and lead to malnutrition and renal bone disease.**
- **The risk of developing complications increases progressively as renal function is lost.**
- **Discussion about the issue of dialysis should occur early to allow time for education, vaccination, preservation of veins and appropriate choices concerning dialysis options, transplantation or conservative management.**
- **Patients with chronic renal failure should have a realistic expectation of the outcomes of dialysis. It is not the solution for all patients.**
- **The presence of multiple comorbidities precludes kidney transplantation in many patients. Due to decreasing deceased donor rates more live donor than deceased donor kidney transplantations are now being performed.**
- **Conservative management, in which medical management is undertaken to control the consequences of renal impairment, is a valid option for some patients with end-stage renal disease.**





Figures 1a and b. a (left). Vascular calcification in a patient with chronic kidney disease. Note the outline of the blood vessels. b (right). Surgical amputation of the great toe for gangrene, a complication of vascular calcification.

Metabolic acidosis

Metabolic acidosis has many adverse effects. Most importantly, it results in muscle wasting and malnutrition as it accelerates protein catabolism and hence patients cannot utilise dietary protein. Malnourished patients commencing dialysis have a far greater risk of morbidity and mortality.

Other conditions that metabolic acidosis contributes to are hyperkalaemia (as the body shifts hydrogen ions intracellularly in exchange for potassium) and renal bone disease (as the body utilises bone as a source of buffer). It also contributes to the sensation of breathlessness as the body compensates by increasing respiratory rate in an attempt to blow off carbon dioxide. Also, left ventricular function is impaired in the presence of a metabolic acidosis.

A falling serum bicarbonate level usually indicates the development of metabolic acidosis. As soon as the patient's serum bicarbonate drops below 21 mmol/L, sodium bicarbonate (Sodibic) should be commenced. If the acidosis is mild, generally one capsule (840 mg) twice a day will be sufficient to maintain serum bicarbonate between 22 and 28 mmol/L. The dose should be titrated as required to maintain the bicarbonate within this target range. As the renal function deteriorates the dose may rise to nine capsules per day or more; generally this increase will be in consultation with the renal physician. The beneficial impact of correcting metabolic acidosis exceeds any concern about the sodium load from using oral sodium bicarbonate.

Renal bone disease

Renal bone disease is not a single entity. It develops as a result of some or all of vitamin D deficiency, hyperparathyroidism, metabolic acidosis and iatrogenic factors (such as aluminium-containing phosphate binders).

Vitamin D deficiency

Vitamin D deficiency occurs in patients with chronic kidney disease because the final step in the conversion pathway of vitamin D to the active metabolite 1,25-dihydroxyvitamin D, or calcitriol, takes place in the kidney. Vitamin D promotes calcium absorption from the intestine, and therefore a lack of calcitriol results in a falling serum calcium concentration. Lack of calcitriol and a low serum calcium level stimulate the parathyroid glands, contributing to the development of hyperparathyroidism.

Treatment with calcitriol is used to maintain the serum calcium within the low- to mid-normal range. The dose is adjusted to avoid hypercalcaemia. In the early stage of renal impairment this may require only 0.5 µg calcitriol (two capsules) a week but the dose has to be adjusted for each individual.

Table 1. Some phosphate binders used in chronic kidney disease

Phosphate binder	Side effects
Calcium carbonate (Cal-Sup, Caltrate)	Constipation, hypercalcaemia
Calcium carbonate and calcium lactate gluconate (Sandocal)	Constipation, hypercalcaemia
Calcium carbonate and glycine (Titralac)	Constipation, hypercalcaemia
Magnesium aspartate (MagMin)	Diarrhoea, hypercalcaemia
Aluminium hydroxide (Alu-Tab)	Constipation; and potentially anaemia, bone disease and dementia
Sevelamer (Renagel)	Associated with metabolic acidosis
Lanthanum carbonate (Fosrenol)	Concerns about long-term use and possible accumulation of a rare earth metal

Hyperparathyroidism

Calcitriol should also be commenced if the parathyroid hormone (PTH) level rises above the normal range. This will occur before the serum calcium level drops below the normal range, and indicates that the current level of serum calcium is insufficient to suppress the rise in PTH. Monitoring of the PTH level should occur more often as the patient's renal function deteriorates. For dialysis patients, it should be checked initially six-monthly, increasing to third-monthly as renal function deteriorates. The target range for PTH is one of the controversial areas in renal medicine – i.e. whether it should be maintained within the normal range at two to three times the upper limit of the normal range.

Hyperphosphataemia

Phosphate retention also stimulates the development of hyperparathyroidism. Uncontrolled serum phosphate is the major risk factor for the development of vascular calcification and cardiovascular events, particularly when it is combined with an elevated calcium phosphate product (serum calcium x phosphate) greater than 4.0 (Figures 1a and b). Calcitriol treatment should be avoided when the serum calcium and/or phosphate levels are elevated.

Phosphate is present in most foods. Although avoiding foods particularly high in phosphate (such as dairy products and cola drinks) will assist with phosphate control, most patients will require phosphate binders. Phosphate binders must be taken with food: patients should be advised to take the medication after their first bite of food.

The currently available phosphate binders include calcium-based binders, magnesium-based preparations, aluminium hydroxide (Alu-Tab), liquids containing mixtures of the above, sevelamer (Renagel) and lanthanum carbonate (Fosrenol) (Table 1). There are side effects with all of the preparations. Calcium-containing phosphate binders frequently cause constipation, and the limiting factor in their use is the development of hypercalcaemia. Magnesium-containing binders often cause diarrhoea, and magnesium levels should be kept below 1.3 mmol/L. The common side effect of aluminium-based binders is constipation but the potentially serious side effects include anaemia, bone disease due to deposition at the mineralisation front and dementia. Sevelamer, a calcium and aluminium-free cationic exchange polymer, is more expensive than the other agents, although it has recently been listed on the PBS. It is associated with metabolic acidosis, and to date studies have not shown better patient survival compared with use of the other binders. Patients generally require higher doses of sodium bicarbonate when sevelamer is added. Lanthanum carbonate has been reported as being well tolerated when used in patients with hypercalcaemia but clinical use is limited and concerns remain about the impact of long-term use and possible accumulation of this rare-earth metal.

The aim of treatment with phosphate binders is to maintain the serum phosphate level below 1.8 mmol/L, and preferably below 1.6 mmol/L (although this target is difficult to achieve). Ensuring the binders are administered with food can help in the achieving of target levels. The choice of phosphate binding agent depends on the patient's other electrolytes, especially calcium and magnesium. Increasing the hours of dialysis by having daily dialysis or nocturnal dialysis improves phosphate control, and phosphate binders are often then not required, or indeed phosphate supplementation may become necessary. Funding issues currently preclude the use of daily dialysis or nocturnal dialysis for most renal units.

If serum phosphate levels fall to below 1.0 mmol/L, the dose of phosphate binders should be reduced and dietary intake checked as a low phosphate level (and potassium level) in a patient with chronic renal failure or on dialysis indicates that the patient is not eating. The reasons why the patient is not eating should be investigated, and a dietitian involved for advice on dietary supplementation.

Hyperparathyroidism

The management of hyperparathyroidism is initially prevention by control of serum calcium and phosphate concentrations, and vitamin D administration.

Cinacalcet hydrochloride (Sensipar) and paricalcitol (Zemplar) are used to treat hyperparathyroidism, but neither is yet available on the PBS. Cinacalcet hydrochloride acts via the calcium sensing receptor in the parathyroid and reduces levels of PTH, calcium, phosphate and the calcium–phosphate product. Patients

still require phosphate binders and vitamin D but a greater proportion reach target levels for PTH, calcium, phosphate and the calcium– phosphate product. Multinational trials involving several renal units in Australia are currently under way to test the hypothesis that this medication has the potential to significantly reduce the development of vascular calcification and hence, potentially, cardiovascular morbidity and mortality of patients with end-stage renal failure.

If hyperparathyroidism develops despite the above interventions then parathyroidectomy with autotransplantation should be undertaken (all four glands are removed from the neck and the section of one gland is inserted into a pocket made in the muscle in the forearm). Blood samples for subsequent monitoring of PTH levels should be taken from the arm without the implanted gland as the levels will be higher in the arm containing the implant. It is important, therefore, to note into which arm the gland has been implanted; if in doubt, take a blood sample from both arms.

Anaemia

The kidneys produce erythropoietin, which stimulates the bone marrow to produce red cells. Once the estimated glomerular filtration rate (eGFR) drops below 60 mL/min/1.73 m^2, the production of erythropoietin falls and anaemia may develop. The proportion of patients requiring erythropoietin (epoetin [Eprex, NeoRecormon] or darbepoetin [Aranesp]) rises as the eGFR drops. Pathology laboratories now automatically report eGFR calculated based on serum creatinine with every serum creatinine measurement ordered.

Before commencing treatment with erythropoietin other causes of anaemia must be excluded or treated, such as vitamin B_{12} or folate deficiency or gastrointestinal tract bleeding resulting in iron deficiency.

It should be noted that patients with renal impairment have functional iron deficiency. Hence the interpretation of what is normal when iron studies are checked is different for these patients. The target for adequate iron stores is a ferritin level above 100 µg/L or a transferrin saturation of greater than 20%, or both. If the iron indices are below target then intravenous iron (iron polymaltose complex [Ferrosig Injection, Ferrum H Injection], iron sucrose [Venofer]) is given. Oral iron is generally not well tolerated, as doses of at least two iron tablets are day are required. IV iron should not be given if active infection or inflammation is present or there has been recent surgery (within four weeks). Dosing regimens vary: for predialysis patients or patients on peritoneal dialysis, intermittent bolus doses of 500 to 750 mg may be given; for haemodialysis patients (including home haemodialysis patients), smaller doses may be given weekly during dialysis. To minimise the risk of iron overload, the upper limit of ferritin should not exceed 500 µg/L.

Erythropoietin is commenced once the haemoglobin concentration falls to below 100 g/L or the patient has symptomatic heart disease as a result of the anaemia. Patients require referral to a renal physician for erythropoietin treatment as it has a Section 100 (Highly Specialised Drugs) listing and is therefore only available under the Highly Specialised Drugs Program. Many renal units have anaemia coordinators who assist with monitoring of the haemoglobin, train patients to give themselves the injections and communicate any changes in erythropoietin doses to patients, their GPs and community nursing staff. Monthly tests are required to monitor the response to erythropoietin and enable dose adjustments to keep haemoglobin within the target range of 110 to 120 g/L. Raising the haemoglobin concentration to above 130 g/L (i.e. into the normal range) is associated with an increased risk of thrombotic events, including clotting of fistulas and other adverse vascular events.

Dialysis, transplantation and conservative management

Dialysis

Patients who might need dialysis in the future should be referred early to the local renal unit for review and education. Late referral is associated with increased morbidity and mortality.

Simple issues may impact significantly on patient outcomes, such as the timing of hepatitis B vaccination and the preserving of veins for potential fistula formation.

Hepatitis B vaccination must occur early, ideally as soon as patients are advised that dialysis may eventually be needed. If vaccinated early in the development of renal disease, patients are more likely to be able to mount antibody responses. Delaying vaccination until close to dialysis results in many patients not being protected despite repeated courses of the high dose vaccine.

Educating patients to protect their nondominant arm from cannulas or other procedures that damage veins preserves their veins for creation of arteriovenous (AV) fistulas in the future. Utilising the patient's own vessels is associated with longer survival of the fistula and fewer complications compared to using polytetrafluoroethylene (PTFE) grafts. Early creation of an AV fistula avoids the need for catheter (cuffed or noncuffed tunnelled) access for dialysis. Morbidity and mortality rates increase when catheters are used for dialysis access.

Education about dialysis also enables patients and their families to develop a realistic expectation of the procedure. Patients and their relatives are then more likely to accept that dialysis is not the solution for everyone and may adversely impact on quality of life, possibly shortening life rather than prolonging it. This applies, for example, to patients with severe cardiac disease. If a patient cannot walk more than 20 metres because of cardiac disease then dialysis will not solve that problem and may harm, even kill, the patient by imposing additional demands

on the heart. The decisions about dialysis that have to be made by patients and their relatives in emergency situations are much easier to make when the realities of dialysis are already at least partially understood.

Functional ability should be taken into account when considering dialysis. Is the patient managing independently at home? Are they undertaking any form of exercise? The sobering reality for renal units is that the death rate for dialysis patients is about 14 per 100 patient years.[1]

Education about dialysis should be undertaken not just by the renal physician but also by the home dialysis training staff. At times it can be beneficial for the patient and his or her relatives to have the opportunity to speak to other patients and/or their relatives. Some units have a predialysis educator whose role includes education about dialysis options and coordination of matters such as hepatitis B vaccination and timely referral for creation of an AV fistula.

Dialysis choices

Home dialysis options are always the best. These consist of peritoneal dialysis or haemodialysis. Home dialysis enables the patient to retain some control over their life and to be independent of hospital routines, unlike those who have dialysis in hospital or satellite units. At home the timing of dialysis can be adjusted to allow for work or family events (e.g. having the dialysis on a particular day in the afternoon rather than in the morning). Switching shifts in hospital or satellite units is often difficult because of the heavy demand for spaces. Peritoneal dialysis is a good first choice as it preserves residual renal function and the patient training for it is relatively quick at less than two weeks. In contrast, it takes at least six to eight weeks to train a patient to undertake haemodialysis, and generally there should be a back-up person available at home when the patient is undergoing dialysis.

'More, never less!' is a simple message for patients on haemodialysis. Length of time spent dialysing is the key factor contributing to long survival, better nutrition and less morbidity. Patients undertaking five hours of dialysis three times a week have better survival rates than those who undertake 4.5 hours three times a week, and these in turn do better than those undertaking four hours the same number of times a week.

For patients who are unable to dialyse at home, the harsh truth is that many of the hospital and satellite units are full and spaces only become available when patients die. Most patients on the transplant waiting list have dialysis at home and hence a transplant does not free up space within the hospital and satellite units.

Withdrawal from dialysis

Another discussion that needs to occur when dialysis options are discussed is the option of withdrawal from dialysis. Dialysis is an artificial means of keeping patients alive. Ceasing dialysis and allowing death to occur is not suicide; it is accepting the realities of the medical situation.

There should, however, be a very formal process undertaken when the patient expresses a wish to cease dialysis:

- the wish to cease dialysis should not be acted on when that wish is expressed on a single occasion
- the wish to cease should be discussed
- the implications of ceasing dialysis should be discussed
- any matter that may impact on the patient's ability to make a rational decision, such as severe depression, must be excluded or treated
- an independent opinion should be sought, such as from a psychiatrist
- the decision should be discussed on a number of occasions with the patient and his or her family.

If the renal physician and the psychiatrist agree that the patient is making a rational decision, the patient should be referred to the palliative care team and the focus of the discussion changed to when to stop, where the death will occur and the management of symptoms during the dying process.

Withdrawal from dialysis was the cause of 33% of the deaths in dialysis patients in 2006.[1] With the increasing age and comorbidities of patients on dialysis this pattern is unlikely to change.

A significant challenge for renal units is the management of the patient who develops a dementia while on dialysis. The patient who has developed a dementia cannot make a decision about withdrawal from dialysis. This is a circumstance in which Advance Care Plans may assist the renal physician and the patient's family in management decisions.

Transplantation

Deceased donor rates are decreasing and now more live donor than deceased donor kidney transplantations are performed – in NSW, from 1st January to 24th December 2007, there were 95 live donor transplantations compared with 89 deceased donor transplants. The death rate for patients with functioning kidney transplants is about two per 100 patient years (deceased donors, 2.5; live donors, 1.1).[1]

The proportion of patients on dialysis who are on the transplant waiting list is fa lling. With diabetes being the leading cause for patients commencing dialysis and the increasing age of patients on dialysis, the presence of multiple comorbidities precludes transplantation in many patients. Before patients are placed on the deceased donor transplant waiting list they undergo a detailed assessment to identify any contraindications to transplantation. Those on the list are required to undergo regular review of their fitness to remain on the list.

Patients receiving a transplant from a live donor also undergo the detailed assessment of their fitness. Donors are also rigorously assessed, both for medical problems and potential psychological impacts of donation.

The average time patients were on the NSW transplant waiting list in 2006 and 2007 was about seven years. Significant numbers of patients on the various State

continued

Table 2. Summary of management aims for patients with chronic kidney disease*

Correct metabolic acidosis – maintain serum bicarbonate between 22 and 28 mmol/L

- Adjust sodium bicarbonate (Sodibic) dose as required

Maintain haemoglobin between 110 and 120 g/L – do not aim to normalise

- Exclude other causes of anaemia, e.g. vitamin B_{12} or folate deficiency, gastrointestinal tract bleeding
- Add erythropoietin (epoetin [Eprex, NeoRecormon] or darbepoetin [Aranesp]) if haemoglobin <100 µg/L or symptomatic heart disease (renal physician decision)
- Intravenous iron supplementation (iron sucrose [Venofer]) as required to maintain the response to erythropoietin
- If on erythropoietin, monthly full blood count and iron studies to monitor response and adjust dose of erythropoietin and iron

Maintain calcium within low to mid normal range

- Adjust calcitriol dose as required

Maintain phosphate <1.8 mmol/L (preferably <1.6 mmol/L)

- Ensure phosphate binders (calcium carbonate-based [Cal-Sup, Caltrate, Sandocal, Titralac], magnesium aspartate [MagMin], aluminium hydroxide [Alu-Tab], sevelamer [Renagel], lanthanum carbonate [Fosrenol]) are taken with food
- Reduce phosphate binder dose if phosphate level <1.0 mmol/L

Monitor PTH (six-monthly)

- Aim to maintain < 3x upper limit of normal range
- Consider surgical intervention if PTH level exceeds target
- Medical management options include cinacalcet (Sensipar) and paricalcitol (Zemplar)

Maintain normal serum potassium

- Institute a low potassium diet
- Review use of medications that cause potassium retention, e.g. ACE inhibitors (but if essential then continue and add regular doses of sodium polystyrene sulfonate [Resonium A] – discuss with renal physician)

Reduce sodium intake

- Reduce dietary salt intake

Review fluid intake

- Dependent on stage of kidney disease and/or heart failure
- Judge fluid by changes in bodyweight
- Use diuretics if necessary, and not on dialysis

Maintain physical activity and encourage weight loss if obese

- Refer to an exercise physiologist if necessary

Treat hypertension

- Aim for the following blood pressure targets:
  - patients with CKD, <130/80 mmHg
  - patients with proteinuria >1 g/24 hours, <125/75 mmHg
  - patients with diabetes, <125/75 mmHg
  - dialysis patients: <150/90 mmHg pre-haemodialysis and <130/80 mmHg pre-peritoneal dialysis
- Treat with ACE inhibitors or angiotensin receptor blockers
- Consider use of loop diuretics or spironolactone (Aldactone, Spiractin)

If known ischaemic heart disease, treat as per standard management

- Treat with ACE inhibitors, angiotensin receptor blockers, beta blockers, aspirin, lipid-lowering medications

Control blood glucose (HbA_{1c} <7.0%)

- Review metformin dose based on eGFR: cease or monitor very closely if eGFR <50 mL/min/1.73 m^2 because of increased risk of lactic acidosis
- Review/reduce insulin dose as renal function deteriorates

Treat lipids

- As per standard guidelines

Monitor serum albumin

- Low serum albumin level is of grave concern as it is a marker of impaired nutrition and increased risk of death due to infective or thrombotic complications
- Aim for protein intake at lower end of normal, 0.8 g/kg of ideal bodyweight/day for predialysis patients, and 1.2 g/kg/day for dialysis patients

Monitor eGFR

- Use as guide to:
  - reducing dose or ceasing use of certain medications
  - timing of fistula creation and starting of dialysis
  - indication of likely onset of complications of CRF, e.g. anaemia

Vaccinate against hepatitis B early

- Vaccinate with hepatitis B vaccine (Engerix-B, H-B-Vax II) as soon as likely need for eventual dialysis realised, to reduce risk of hepatitis B virus infection while on dialysis

Save arm

- If dialysis likely eventually, protect the nondominant arm from cannulas and suchlike to preserve the veins for future creation of arteriovenous fistulas

Stop nephrotoxins

- Cease use of NSAIDs, including COX-2 inhibitors
- Avoid use of radiographic contrast, especially gadolinium-containing agents, unless essential (then give saline pre- and post-procedure)

Stop smoking

- Smoking tobacco is associated with more rapid loss of renal function and more severe proteinuria

* Some of this management is not discussed in detail in this article. See the article by Dr Lonergan in the February issue of *Medicine Today* – Chronic kidney disease. Part 1: detection and renal function preservation. *Medicine Today* 2008; 9(2): 25-35.

CKD: useful websites

Kidney Health Australia
www.kidney.org.au
Chronic Kidney Disease Management In General Practice is available free to all GPs either on the Kidney Health Australia website or as a printed booklet on request (phone: 08 8334 7555).

CARI guidelines (Caring for Australasians with Renal Impairment)
Link available via Kidney Health Australia website.

The Australian Diabetes, Obesity and Lifestyle (AusDiab) study
www.diabetes.com.au

Australia and New Zealand Dialysis and Transplant Registry
www.anzdata.org.au

and nationwide transplant waiting lists have to be removed as they develop complications of renal disease, in particular vascular disease, or die without having received a transplant.

Conservative management

Conservative management is a valid option for some patients with end-stage renal disease. This does not mean being abandoned by the system but rather that medical management is undertaken to control the consequences of renal impairment. This medical management includes giving erythropoietin to maintain haemoglobin concentrations, treating metabolic acidosis and controlling serum phosphate levels.

The patient should also be referred to a palliative care team for discussion about management options when death approaches. Such options are dying at home with the support of the palliative care team, admission to a hospice or, in some circumstances, admission to hospital for symptom management and support. A well-managed death (and that does not mean euthanasia) can be a positive and rewarding experience for those left behind. We have a responsibility not only to the dying but also to those who remain.

Conclusion

Early identification of patients with renal impairment and aggressive intervention can slow the progression of renal disease and prevent or minimise complications, including the development of cardiovascular disease. Late referral to a renal physician is associated with increased morbidity and mortality. Discussion about the issue of dialysis should occur early to allow for education, vaccination and preservation of veins and appropriate choices concerning dialysis options, transplantation or conservative management.

The management aims for patients with chronic kidney disease are summarised in Table 2 and internet sources of management information are given in the box on this page. MT

Reference

1. Australia and New Zealand Dialysis and Transplant Registry. ANZDATA Registry Report 2007. McDonald S, Chang S, Excell L, eds. Adelaide: ANZDATA Registry; 2008.

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