Early renal impairment
the role of the GP

General practice management is appropriate for patients with early stage renal impairment who are at low risk of progression to end stage renal failure. Investigation of patients is aimed primarily at determining their level of risk, rather than the causative pathology.

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Approximately 1500 people develop end stage renal disease (ESRD) each year in Australia. Most will have had early renal impairment (glomerular filtration rate [GFR] reduced but greater than 30 mL/min) for many years, often without realising they have a health problem. Appropriate treatment could have slowed or prevented their progression to ESRD. In this article we outline the epidemiology of early renal impairment in Australia, identify the known risk factors and describe an evidence-based approach to its detection and management in general practice. We have based this article on the research evidence summarised in the websites listed in the box 'Useful resources' on page 21 and on other authoritative sources.

Epidemiology

The AusDiab study, a cross-sectional survey of a representative sample of over 11,000 Australian adults aged 25 years or over, found that 2.5% had proteinuria and 1.1% had a serum creatinine of over 120 µmol/L.[1] This implies that several hundred thousand Australians have significant early renal impairment. In rural and remote Aboriginal communities, almost 25% of adults have proteinuria. A Japanese study indicates that people with proteinuria are 15 times more likely than people without proteinuria to develop ESRD within 10 years.[2]

A number of risk factors have been identified for renal impairment (Table 1). Indigenous Australians constitute less than 2% of the population but almost 10% of patients commencing treatment for ESRD. A family history features in most of the leading causes of ESRD, including diabetes, familial types of glomerulonephritis, hypertension and polycystic kidney disease. In the Multiple Risk Factor Intervention Trial (MRFIT

IN SUMMARY

- **Patients at risk of early renal impairment should be offered annual screening for proteinuria.**
- **Renal function can be estimated from serum creatinine using the modified Cockcroft-Gault formula.**
- **Patients with early renal impairment should be advised to stop smoking, take regular exercise and maintain a normal protein intake.**
- **Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors should be avoided in early renal impairment. ACE inhibitors, angiotensin II receptor antagonists, diuretics and radiological contrast agents should be prescribed with care.**
- **Strict control of blood pressure and careful management of proteinuria, diabetes and anaemia improve outcomes for patients with early renal impairment.**
- **Patients with severe renal impairment should be referred promptly to a nephrologist. Referral should also be considered for younger patients or if renal function is declining rapidly, proteinuria is heavy, there is significant comorbidity or treatment targets prove difficult to achieve.**

Table 1. Risk factors for early renal impairment in Australia

Aboriginal or Torres Strait Islander
Aged 50 years or over
Diabetes mellitus
Family history of renal disease
High blood pressure
Cigarette smoker

study) over 300,000 men in the USA were screened and followed up for an average of 16 years. Older age, smoking, hypertension and diabetes were found to be major risk factors for ESRD.[3]

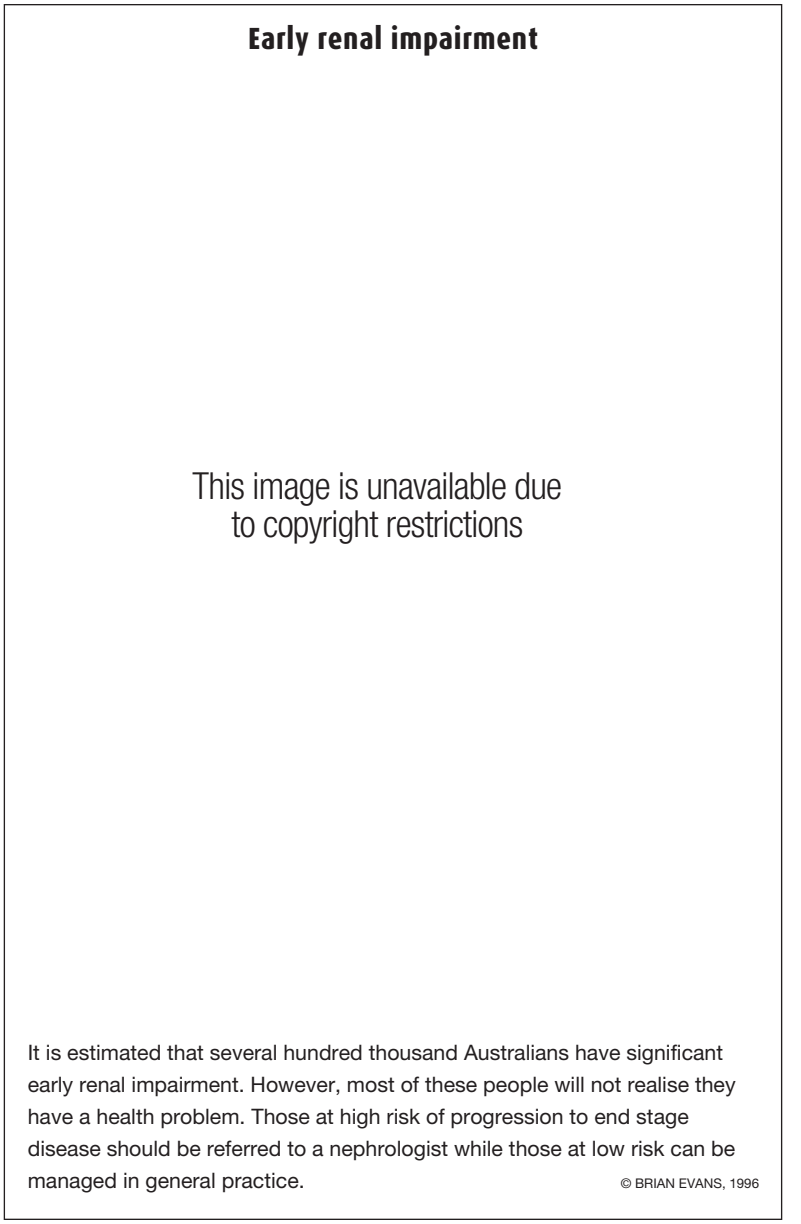
Detection and investigation

Urine testing

The best single screening test for early renal impairment is dipstick testing for proteinuria – a cheap test with immediate results (Figure 1). There is a strong correlation between raised urinary protein excretion and progression towards renal failure. Furthermore, interventions that slow the progress of renal disease seem to be most effective in those patients with the worst proteinuria.

Although universal population screening for proteinuria is not currently considered worthwhile, all patients with one or more risk factors for early renal impairment should be offered annual dipstick testing. Dipstick testing for proteinuria is inadequate, however, for people with diabetes; these people require their urinary albumin excretion rate to be measured at least annually (see below).

Early renal impairment



It is estimated that several hundred thousand Australians have significant early renal impairment. However, most of these people will not realise they have a health problem. Those at high risk of progression to end stage disease should be referred to a nephrologist while those at low risk can be managed in general practice.

Useful resources

CARI Guidelines: Caring for Australians with Renal Impairment
http://www.kidney.org.au/cari

New Zealand Guidelines Group: Primary care guidelines for the management of core aspects of diabetes care
http://www.nzgg.org.nz/library/gl_complete/diabetes/index.cfm#contents

National Heart Foundation of Australia: Guide to management of hypertension for doctors
http://www.heartfoundation.com.au/prof/index_fr.html

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Figure 1. Dipstick testing of urine will reveal proteinuria and other abnormalities.

Table 2. Interpretation of urinary albumin to creatinine ratios (ACR)

ACR (g/mol)	Daily protein excretion	Nomenclature
<3.4	<30 mg	Normal
3.4 to 34	30 to 300 mg	Microalbuminuria
>34*	>300 mg	Proteinuria
>300	>3 g	Proteinuria – nephrotic

Urinary albumin is in mg/L; urinary creatinine is in mmol/L.
* Patients with an ACR >34 g/mol usually have a positive dipstick test for proteinuria.

Dipstick positive – what next?

Dipstick testing has a specificity of about 85% in detecting proteinuria (urinary protein excretion greater than 300 mg in 24 hours). This means that the test will be falsely positive in approximately 15% of people who do not have proteinuria. It is important, therefore, to check dipstick results by quantifying the protein excretion in any patient whose dipstick test is positive.

The gold standard for determining protein excretion is measurement of the total amount of protein in a 24-hour urine specimen. However, reliable collection of the complete specimen is often impractical. An easier alternative (which also has excellent precision) is measurement of the albumin:creatinine ratio (ACR) in an early morning urine specimen. Table 2 lists the protein excretion rates corresponding to various ACR ranges and the nomenclature used for each. The patient's blood pressure should be checked (if this has not been done already), and blood should be sent for measurement of serum levels of urea, creatinine and electrolytes.

Most dipsticks also test the urine for substances other than protein. If other abnormalities are detected, then they should be followed up appropriately. If leucocytes or nitrites are detected, a midstream specimen should be obtained for culture. The dipstick test for protein should be repeated after treatment of any infection. The presence of blood in the urine is always an abnormal finding, and should lead to appropriate investigation and referral.

Dipstick negative

The sensitivity of dipstick testing for proteinuria is about 80%. This means that approximately 20% of people who do, in fact, have proteinuria will have a falsely negative dipstick test. Therefore, people with the risk factors listed in Table 1 should be tested annually, and any modifiable risk factors (hypertension, diabetes and smoking) should be managed appropriately.

Glomerular filtration rate

The single most meaningful measure of renal function is the glomerular filtration rate (GFR). Its direct measurement is inconvenient, but it can be estimated from the serum creatinine level using the

The modified Cockcroft-Gault formula

For women: Estimated GFR (mL/min) = $\frac{(140\text{-age [in years]}) \times \text{weight (in kg)}}{\text{serum creatinine (µmol/L)}}$

For men: Calculate estimated GFR as for women, and then multiply by 1.23.

The modification is an arithmetic simplification of the original formula. The GFR estimate obtained will be 4% lower for women and unchanged for men, compared with an estimate obtained using the original formula.

'Think GFR, not serum creatinine'

Ms AT is aged 58 years and weighs 55 kg. Her serum creatinine is 107 µmol/L, which is well within the laboratory's stated normal range of 60 to 130 µmol/L. However, her GFR, as estimated by the modified Cockcroft-Gault formula, is:

$$(140 - 58) \times 55/107 = 42 \text{ mL/min.}$$

This value is well below the lower limit of normal for GFR of 80 mL/min, indicating that Ms AT has significant renal impairment despite her normal serum creatinine level.

modified Cockcroft-Gault formula (see the box on page 22). This formula utilises the patient's serum creatinine level, age, weight and sex. A number of computerised clinical record systems include a calculator for the Cockcroft-Gault formula.

Interpreting the serum creatinine

The normal range for GFR in adults is over 80 mL/min. It is important to note that a patient with a normal serum creatinine concentration can still have significant renal impairment – remember to 'think GFR, not serum creatinine' (see the box on page 22). Patients whose GFR is reduced but is greater than 30 mL/min are said to have early renal impairment. Patients with GFR less than 30 mL/min have severe renal impairment and are at high risk of progression to ESRD: they should be referred promptly to a nephrologist.

The Cockcroft-Gault formula does not always give an accurate estimate of GFR. In patients with severe renal impairment, decompensated cirrhosis or obesity, the formula may overestimate the GFR, while in patients with cancer, it may underestimate GFR. Clinically important errors can arise in patients with these conditions.

Management

Patients with early renal impairment are at risk of progression to ESRD but this risk can be substantially reduced by appropriate management by their GP. Key aspects of the management are listed in Table 3 and are described in more detail below.

Stop smoking

Smokers with renal disease progress to renal failure more rapidly than do non-smokers. In addition to many other health benefits, stopping smoking slows the rate of progression, at least in diabetic renal disease. Smokers with early renal impairment should be encouraged to stop, and assisted in doing so.

Drugs to watch

Several commonly prescribed medications may exacerbate renal impairment (Table 4). Nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors should be avoided if at all possible. Although angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and diuretics are key medications in the management of progressive renal disease, hypertension and heart disease, their use must be carefully monitored because they may exacerbate renal impairment in certain situations.

Radiologists should be alerted to patients with renal impairment, so that they can use appropriate preventive strategies when the use of contrast agents is indicated.

No protein restriction

Traditionally, patients with renal disease were recommended a low protein diet. However, the impact on progression was minimal and many patients became malnourished. Patients with early renal impairment should consume the normal recommended daily intake of 0.75 to 1.0 g protein per kg bodyweight.

Exercise

Exercise does not appear to slow the progress of renal insufficiency, but the evidence on this point is weak. Given its other benefits, patients with early renal impairment should be advised to take regular exercise.

Immunisation

The NHMRC currently recommends annual influenza immunisation for patients with diabetes, renal dysfunction or other chronic illness requiring regular medical follow up. Pneumococcal vaccination is also recommended for patients with diabetes or chronic renal disease.

Strict control of blood pressure

Strict control of blood pressure slows the progression of renal impairment, as well as reducing cardiac and cerebrovascular complications. The blood pressure targets currently recommended for patients with early renal impairment are below 120/75 mmHg for patients under 50 years of age, and below 130/85 mmHg for those over 50. Achieving these targets usually requires the use of more than one antihypertensive drug (Table 5).

Table 3. Management of early renal impairment in general practice

Address smoking
Avoid NSAIDs and COX-2 inhibitors
Advise normal protein intake
Recommend regular exercise
Consider immunisation requirements
Treat hypertension
Treat proteinuria
Monitor ACE inhibitor or angiotensin II receptor antagonist use
Manage diabetes
Address anaemia

ACE inhibitors

ACE inhibitors are particularly effective in protecting renal function. They can usually be started in general practice, being generally safe and well tolerated. Potential risks are first dose hypotension, hyperkalaemia and worsening of renal impairment in patients with renal artery stenosis. However, in randomised, controlled trials

Table 4. Commonly prescribed drugs that may worsen renal impairment

NSAIDs
COX-2 inhibitors
Diuretics
ACE inhibitors and angiotensin II receptor antagonists
Contrast agents

of ACE inhibitors against placebo, rates of drop-out due to adverse effects have been extremely low.

First dose hypotension is a potential risk in patients who are hypovolaemic (e.g. due to diuretic treatment), have severe hypertension or are elderly. The initial dose should be low for all patients (especially the elderly) and diuretics should, if possible, be withheld for two to three days before commencing therapy. If this is not possible, the patient may require hospitalisation to start treatment.

The patient's serum potassium should be known before an ACE inhibitor is prescribed. Serum potassium, urea and creatinine should be checked about seven days later and again at four and eight weeks. A rise in serum creatinine of greater than 30% above baseline within the first two months of commencing treatment is considered significant, and the patient should be advised to stop the ACE inhibitor immediately.

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists are appropriate alternatives for patients who cannot tolerate an ACE inhibitor because of troublesome cough or other side effect. Like ACE inhibitors, this class of drugs has renoprotective properties but can cause both hyperkalaemia and deterioration in renal function.

Nondihydropyridine calcium antagonists

Nondihydropyridine calcium antagonists such as diltiazem or verapamil, which also have renoprotective properties, may be prescribed for patients who can tolerate neither an ACE inhibitor nor an angiotensin II receptor antagonist.

Combinations of antihypertensive drugs

Most patients with early renal impairment will not achieve target blood pressures despite taking the maximum recommended dose of a single agent. Possible reasons that should be excluded are 'white coat hypertension', inappropriate sphygmomanometer cuff size, poor compliance with therapy, high salt intake, heavy alcohol consumption and intake of medication that exacerbates hypertension (such as an NSAID). If these factors are excluded, then a second drug is needed.

For patients taking an ACE inhibitor or angiotensin II receptor antagonist, the addition of a nondihydropyridine calcium antagonist, a β-blocker or a nonpotassium-sparing diuretic may be appropriate. A patient taking diltiazem may be prescribed a β-blocker, but the combination of a β-blocker with verapamil can be dangerous and should be avoided.

Treatment of proteinuria

Both ACE inhibitors and angiotensin II receptor antagonists slow the progress of renal impairment in patients with proteinuria, even in the absence of hypertension. Intervention is beneficial for patients

Table 5. Antihypertensive drugs used in early renal impairment

ACE inhibitors
Captopril (Acenorm, Capoten, Captohexal, Topace)
Enalapril (Alphapril, Amprace, Auspril, Enahexal, Renitec)
Fosinopril (Monopril)
Lisinopril (Fibsol, Lisodur, Prinivil, Zestril)
Perindopril (Coversyl)
Quinapril (Accupril, Asig)
Ramipril (Ramace, Tritace)
Trandolapril (Gopten, Odrik)

Angiotensin II receptor antagonists
Candesartan (Atacand)
Eprosartan (Teveten)
Irbesartan (Avapro, Karvea)
Losartan (Cozaar)
Telmisartan (Micardis, Pritor)

Nondihydropyridine calcium antagonists
Diltiazem (Auscard, Cardizem, Coras, Diltahexal, Dilzem, Vasocardol)
Verapamil (Anpec, Cordilox, Isoptin, Veracaps, Verahexal)

Combinations of drugs
The following combinations of drugs may be used:
- ACE inhibitor plus nondihydropyridine calcium antagonist, β-blocker or nonpotassium-sparing diuretic
- Angiotensin II receptor antagonist plus nondihydropyridine calcium antagonist, β-blocker or nonpotassium-sparing diuretic
- Diltiazem plus β-blocker

Nonpotassium-sparing diuretics
Bendrofluazide (Aprinox)
Chlorthalidone (Hygroton)
Hydrochlorothiazide (Dichlotride)
Indapamide (Dapa-Tabs, Indahexal, Insig, Napamide, Natrilix)

Beta blockers
Atenolol (Anselol, Atehexal, Noten, Tenormin, Tensig)
Metoprolol (Betaloc, Lopresor, Metohexal, Metolol, Minax)
Oxprenolol (Corbeton)
Pindolol (Barbloc, Visken)
Propranolol (Deralin, Inderal)

Preparations containing two antihypertensive agents
ACE inhibitor plus diuretic:
- Accuretic (quinapril plus hydrochlorothiazide)
- Coversyl Plus (perindopril plus indapamide)
- Monoplus (fosinopril plus hydrochlorothiazide)
- Renitec Plus 20/6 (enalapril plus hydrochlorothiazide)

Angiotensin II receptor antagonist plus diuretic:
- Atacand Plus 16/12.5 (candesartan plus hydrochlorothiazide)
- Avapro HCT (irbesartan plus hydrochlorothiazide)
- Karvezide (irbesartan plus hydrochlorothiazide)

with proteinuria of more than 1 g/day, which is equivalent to an ACR of more than 100 g/mol. Therefore, a drug in one of these classes should be considered for any patient with early renal impairment and proteinuria, irrespective of their blood pressure. The initial dosage should be low and subsequently increased as tolerated. Used in this manner, treatment should not cause symptomatic hypotension. In non-diabetic patients, the treatment should be titrated against the level of proteinuria, with the aim of reducing protein excretion to less than 1 g per day (urinary ACR of less than 100 g/mol).

Renal damage in diabetes

One of the first clinical indicators of renal damage in both types 1 and 2 diabetes is microalbuminuria (24-hour albumin excretion in the range 30 to 300 mg). Therefore, patients with diabetes should be treated at much lower levels of albumin excretion than are other at-risk patients. An ACE inhibitor or angiotensin II receptor antagonist should be prescribed for any patient with diabetes and either microalbuminuria or macroalbuminuria. These classes of drug are also the first choice for control of high blood pressure, even if urinary protein excretion is normal. On present evidence, patients with diabetes who have neither hypertension nor microalbuminuria should not routinely be prescribed one of these drugs.

Control of hyperglycaemia is also important in slowing the progress of renal disease. The currently recommended targets are preprandial blood glucose concentrations in the range 4.4 to 6.7 mmol/L and glycosylated haemoglobin (HbA_{1c}) less than 7%.

Anaemia

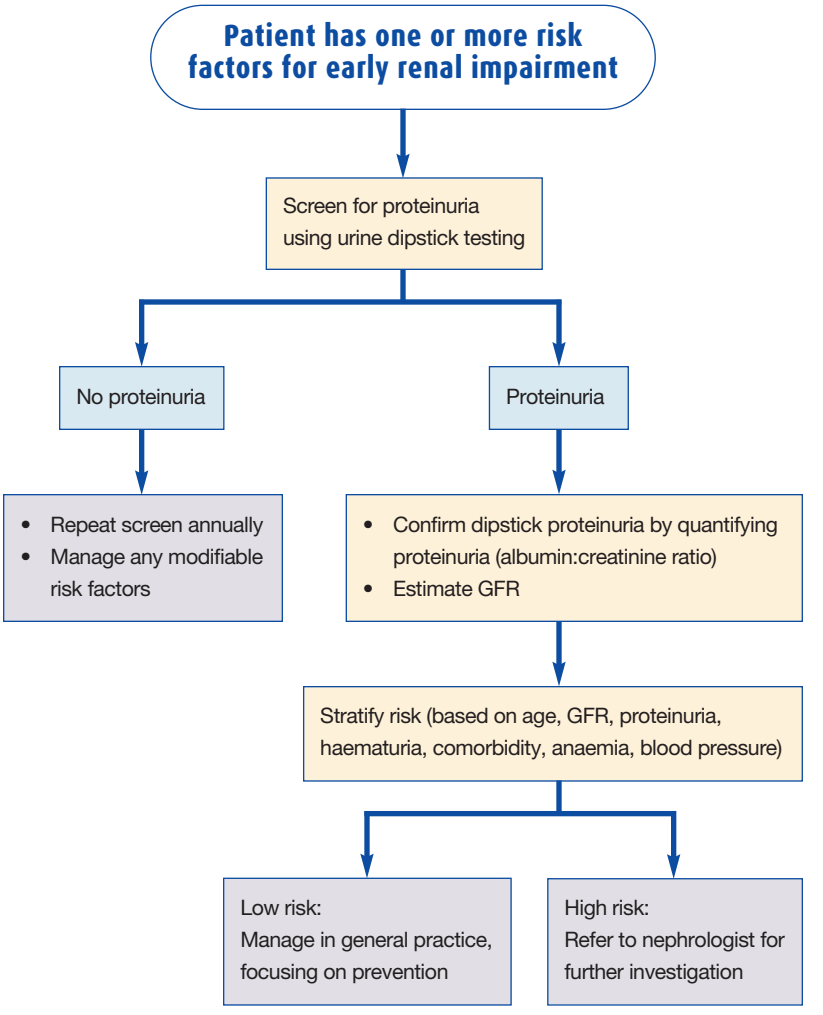
Anaemia may be a consequence of chronic renal impairment and often develops early in the course of renal impairment. Once other causes have been excluded, iron or erythropoietin (darbepoetin [Aranesp], epoetin [Eprex]) therapy, or both, to achieve a haemoglobin concentration above 100 g/L enhances quality of life, reduces breathlessness and lethargy, and improves exercise tolerance. Referral to a hospital-based specialist, usually a nephrologist, is necessary to commence erythropoietin therapy.

Working with the patient

The patients and their families do most of the work of managing renal disease. We have not found any studies relating specifically to early renal impairment but research has clearly demonstrated the importance of four elements of health care in helping patients manage chronic illness.[4] These elements, as applied to early renal impairment are summarised below.

- **Collaborative problem definition.** The patient and his or her doctor need to develop a shared appreciation of the problems and issues to be addressed. It is the responsibility of the doctor to explain relevant aspects of what is known about early renal impairment and its management, and to explore with the patient his or her

Risk-based management of renal impairment



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understanding, concerns, preferences and expectations of care.

- **Prioritising, goal setting and planning.** The doctor should work with the patient in identifying the issues of greatest importance to each of them, in setting achievable goals (e.g. to stop smoking or to control hyperglycaemia) and in developing a realistic action plan to address these goals.
- **Education and support.** Patients and their families need information about early renal impairment and its treatment, help in lifestyle modification and support in coping with the emotional demands and practical implications of the condition.
- **Active and sustained follow up.** Patients with early renal impairment should be seen regularly in the practice, preferably by the same doctor each time, and attempts should be made to contact patients who miss their appointments.

Indications for referral

Patients with a GFR below 30 mL/min should be referred promptly to a nephrologist. Referral should also be considered for patients aged less than 35 years, those whose GFR is above 30 mL/min but declining rapidly, those with proteinuria of more than 3 g/day and those with significant comorbid illness or evidence of a systemic disease such as systemic lupus erythematosus. Referral should also be considered for patients who do not reach targets for blood pressure or protein excretion within six months (Table 6).

Conclusion

Traditionally, patients with signs of organ dysfunction are offered investigation to ascertain the causative pathology, to assess the severity of the disease process and to guide appropriate therapy. There is no evidence, however, that all patients benefit from intensive investigation of early renal impairment. Instead, the evidence supports the paradigm in the flowchart on page 29. Investigation of the patient at risk should be aimed primarily at stratification. Patients at high risk of progress towards ESRD should be referred to a nephrologist for further investigation while patients at low risk can be managed in general practice, with the aim of preventing further renal damage and avoiding progression to renal failure. MT

Table 6. When to consider referral to a nephrologist

Age less than 35 years
Estimated GFR less than 30 mL/min
GFR greater than 30 mL/min but declining rapidly
Nephrotic-range proteinuria (greater than 3 g/24 hours)
Haematuria present
Significant comorbidity or systemic illness
Anaemia due to renal impairment
Failure to reach targets for blood pressure or protein excretion within six months

Acknowledgements

The authors would like to thank David Johnson, Steve Kalowski and David Tiller for their comments on this article.

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