

# How to **treat**

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## Background

DRUGS are a common cause of kidney dysfunction. Most often they cause potentially reversible acute kidney failure, but gradual-onset, irreversible, chronic kidney disease also occurs.

For example, Australia historically has one of the highest rates of analgesic nephropathy in the world related to past use of Bex and Vincent's powders, and many affected patients require chronic dialysis.

Drugs can influence kidney function in three main ways:

- Acute elevations of plasma urea and creatinine concentrations.
- Potentially life-threatening electrolyte imbalances.
- Progression to chronic kidney disease with its inherent complications.

The relationship between drugs and the kidney is complex but can be approached from two perspectives: identifying drugs that cause or contribute to kidney dysfunction (see Pathogenesis, p32, and table 2, p33), and modifying the use of certain drugs in patients with acute kidney failure or chronic kidney disease (see Prescribing for patients with impaired kidney function in part 2, next week).

### Definitions and epidemiology

No consensus exists on how best to define acute kidney failure, but a useful definition for day to day use is:

*cont'd page 31*



# KIDNEY COMPLICATIONS OF COMMONLY USED DRUGS – PART 1

## inside

**Pathogenesis of drug-induced kidney failure**

**Drugs responsible for renal complications**

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from page 29

■ If the baseline plasma creatinine concentration is  $<220\mu\text{mol/L}$ , an abrupt rise of more than  $50\mu\text{mol/L}$  (normal range  $40\text{--}110\mu\text{mol/L}$ ) compared with a previous baseline measurement.

Or

■ If the baseline is  $>220\mu\text{mol/L}$ , an abrupt rise of more than 20% compared with a previous baseline measurement.

These are convenient but insensitive measures of kidney function because the GFR must fall by about 50% below the normal range before the plasma creatinine concentration rises outside the normal range. Conversely, a large increase in plasma creatinine concentration may result from a relatively small decline in GFR in patients with pre-existing chronic kidney disease.

Although it is not known how often acute kidney failure occurs in the primary care setting, 1-5% of hospital admissions, 5-15% of patients undergoing CABG and about 25% of patients admitted to intensive care units are affected.

About 16% of adult Australians aged  $>25$  have at least one indicator of chronic kidney disease (proteinuria or reduced kidney function). Generally these patients are at increased risk of progressing to end-stage kidney disease and suffering adverse outcomes, particularly adverse cardiovascular outcomes.

Chronic kidney disease is frequently under-recognised and may be present in patients whose plasma creatinine concentration is within the so called normal range ( $40\text{--}110\mu\text{mol/L}$ ).

An important development in recent years has been the creation of a simple staging system defining chronic kidney disease (table 1). A recent initiative by the Australasian Creatinine Consensus Working Group, based on this staging system, recommends that asymptomatic patients be identified using automatic reporting by all pathology laboratories of estimated GFRs (eGFRs) for all patients with rates  $<60\text{mL/min/1.73m}^2$  (ie, normalised to body surface area), while those with rates  $>60\text{mL/min/1.73m}^2$  will be reported as "eGFR  $>60\text{mL/min/1.73m}^2$ ".

The relevance of this development is that it helps identify patients with overt and subclinical chronic kidney disease who may be at increased risk of kidney complications of commonly used drugs.

Although useful, eGFRs are calculated using an equation called the abbreviated MDRD<sup>2</sup> equation, which does not require the patient's weight. They must be interpreted with caution, as they

have not yet been adequately validated in patients of Asian origin or in Indigenous Australians.

The estimation also lacks precision in extremes of

body size and age (see Authors' case study, The pitfalls of eGFR, p34).

When doubt remains, more traditional methods such as the Cockcroft-Gault

equation (available as an inbuilt renal function calculator in most medical practice software packages) or an accurate 24-hour collection of urine for protein and cre-

atinine clearance can be used. However, these tests are less reliable in the acute setting because they rely on measurements of serum creatinine, which may vary from day to day.

### Normal renal autoregulation

Central to understanding some of the potentially harmful effects of several commonly used drugs is an understanding of the normal autoregulatory mechanisms the body uses to maintain kidney perfusion. If these mechanisms fail or if the patient remains untreated, pre-renal acute kidney failure may develop and ultimately progress to acute tubular necrosis (figure 1).

In times of haemodynamic instability, preservation of intraglomerular pressure is partly dependent on enhanced prostaglandin synthesis. This prostaglandin synthesis contributes to afferent arteriolar vasodilation, which maintains forward flow of blood into the kidney and preserves GFR.

Through their effects on endogenous prostaglandin synthesis, ingestion of NSAIDs, including COX-2-selective NSAIDs, during haemodynamic instability inhibits these protective autoregulatory mechanisms and often contributes to acute kidney failure.

Similarly, angiotensin-II secretion helps preserve intraglomerular pressure and maintenance of GFR by preferentially inducing efferent arteriolar vasoconstriction. Ingestion of ACE inhibitors or angiotensin-II-receptor antagonists (ARAs) inhibits this protective autoregulatory mechanism (figure 2) and may contribute to acute kidney failure, particularly in patients with bilateral renal artery stenosis, or unilateral renal artery stenosis in patients with a unilateral functioning kidney. The use of ACE inhibitors and ARAs in patients with chronic kidney disease is discussed in part 2.

### Patients at increased risk of kidney dysfunction

Patients with chronic kidney disease of any cause are at greater risk of developing acute-on-chronic kidney dysfunction. Conditions that increase this risk include:

- Severe congestive cardiac failure.
- Chronic hypertension.
- Diabetes mellitus.
- Bladder outflow obstruction.
- Hepatic dysfunction.
- Multiple myeloma.
- Hypercalcaemia.
- Chronic generalised vasculopathy.

Great care must be taken when managing and prescribing for these patients, even when plasma creatinine concentrations remain in the normal range.

Figure 1: Pre-renal acute kidney failure and ischaemic acute tubular necrosis are intimately related, forming a continuum of manifestations of renal hypoperfusion. (Adapted from Thadhani R, et al.<sup>3</sup>)

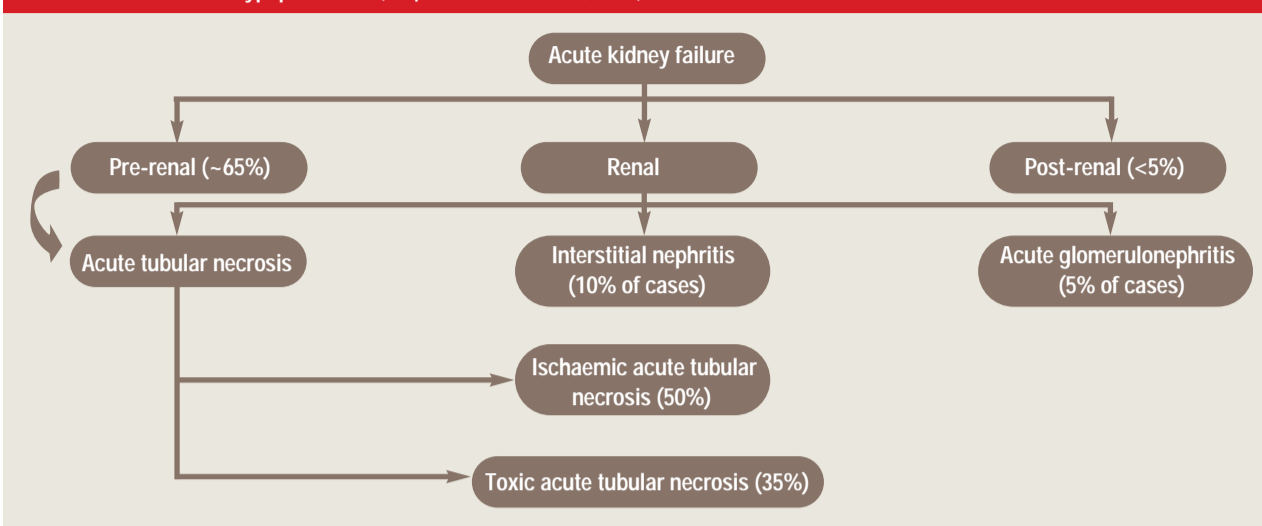


Figure 2: Effects of NSAIDs, ACE inhibitors and angiotensin-II-receptor antagonists (ARAs) on kidney protective autoregulatory mechanisms.

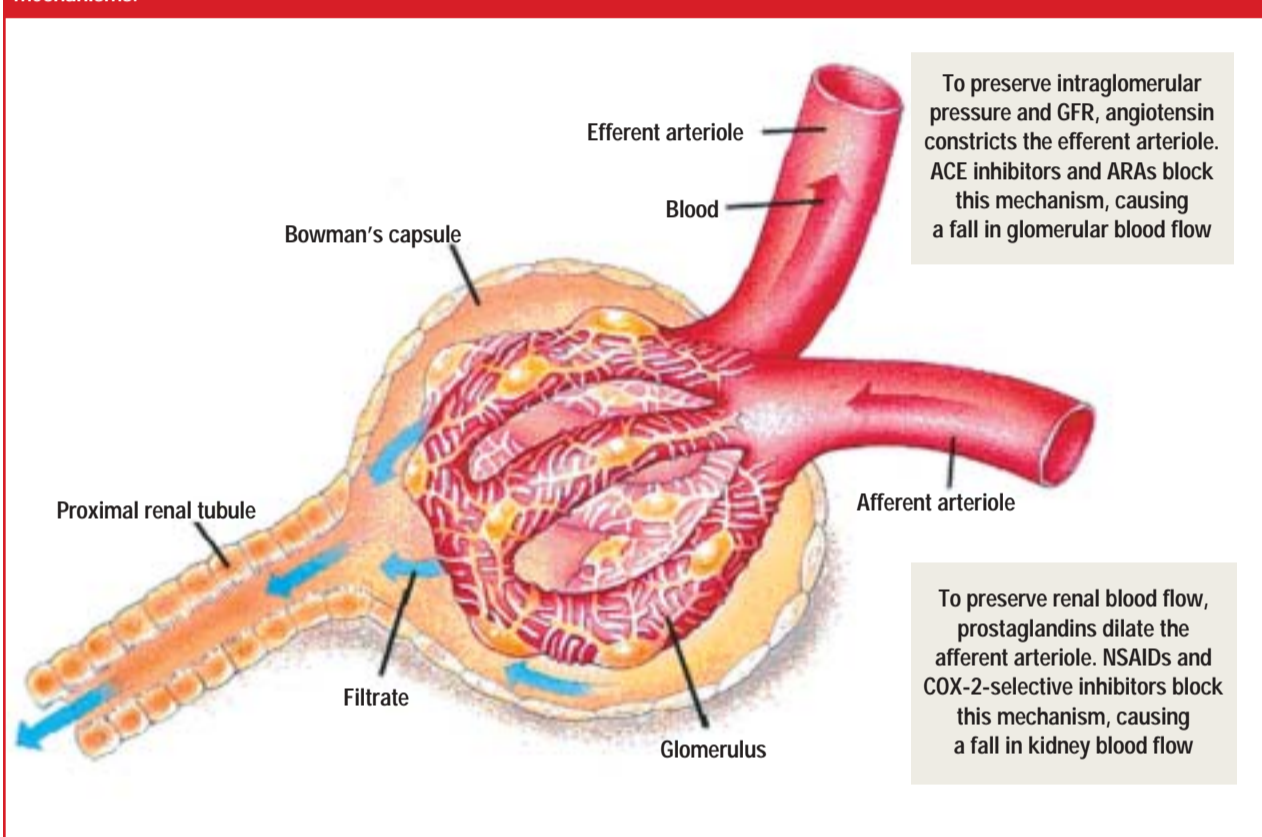


Table 1: Kidney Disease Outcomes Quality Initiative<sup>1</sup> classification of chronic kidney disease (CKD)

Stage	Definition	GFR* (mL/min/1.73m <sup>2</sup> )	Prevalence in Australia (%)	Management plan
1 <sup>†</sup>	CKD with normal GFR	$>90$	0.9	<ul style="list-style-type: none"> <li>■ Screen for CKD</li> <li>■ Diagnose and treat cause</li> </ul>
2 <sup>†</sup>	CKD with mild decrease in GFR	60-89	2.0	<ul style="list-style-type: none"> <li>■ Screen for CKD</li> <li>■ Diagnose and treat cause</li> </ul>
3	CKD with moderate decrease in GFR	30-59	10.9	<ul style="list-style-type: none"> <li>■ As above plus estimate rate of progression</li> <li>■ Optimise kidney and cardiovascular risk factors</li> <li>■ Avoid nephrotoxic drugs</li> <li>■ Initiate antiproteinuric, renoprotective drugs (ACE inhibitor and/or angiotensin-II-receptor antagonist if appropriate)</li> <li>■ Evaluate and treat complications of CKD (consider referral to nephrologist)</li> </ul>
4	CKD with severe decrease in GFR	15-29	0.3	<ul style="list-style-type: none"> <li>■ As above plus refer to nephrologist</li> <li>■ Assess suitability for dialysis and/or kidney transplant</li> </ul>
5	CKD with severe decrease in GFR	$<15$	0.003	<ul style="list-style-type: none"> <li>■ As above and institute dialysis and/or kidney transplant</li> <li>■ Address end-of-life issues if renal replacement therapy inappropriate</li> </ul>

\*GFR is normally  $125\text{mL/min/1.73m}^2$  for a 30-year-old and falls by about  $8\text{mL/min/1.73m}^2$  per decade thereafter

<sup>†</sup>CKD defined by a urine albumin:creatinine ratio  $>3.4\text{mg/mmol}$  on two spot urine tests or scarring on renal imaging

## Pathogenesis

DRUGS can exert their nephrotoxic effects in a variety of ways ranging from the commonplace to the obscure (table 2 and figure 3).

The most common scenario is overly enthusiastic use of diuretics and/or antihypertensive medications, which can lead to dehydration and/or hypotension, resulting in reduced GFR and acute kidney failure. These effects are synergistic and likely to be worse if caused by ACE inhibitors or ARAs.

Similarly, simultaneous administration of NSAIDs, including COX-2-selective inhibitors, will often be detrimental in patients with co-existent dehydration, because of impaired protective autoregulatory mechanisms (see Authors' case study, 'The triple whammy', p34).

Importantly, most cases of haemodynamically mediated acute kidney failure result from a combination of insults combined with impaired autoregulatory mechanisms. Patients at particularly high risk for haemodynamically induced 'ischaemic' acute tubular necrosis include all patients with potentially compromised kidney perfusion (eg, hypotension of any cause), congestive cardiac failure, hepatic cirrhosis or nephrotic syndrome.

Acute allergic tubulo-interstitial nephritis (figure 4) is an uncommon cause of acute kidney failure and can be caused by a broad range of commonly used drugs (figure 3): research suggests that proton-pump inhibitors are the most common cause. Although this adverse reaction is rare, these agents are the third most frequently prescribed class of drugs in Australia.

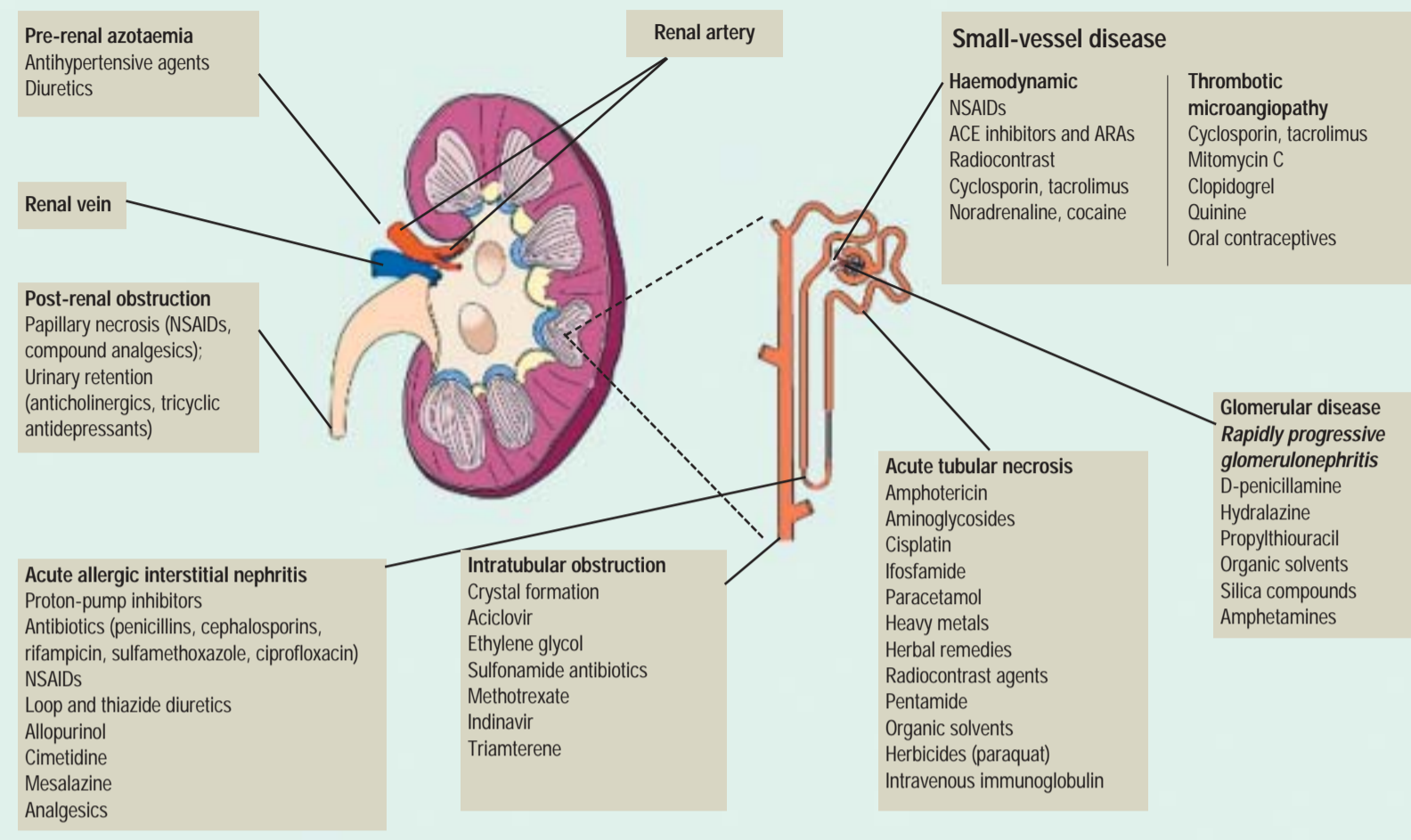
Clinically significant myositis occurs in 0-0.25% of patients taking statins, the drugs prescribed most often on the PBS, and all patients should be encouraged to seek immediate medical attention should they develop muscle tenderness or pain while taking them.

In severe cases, rhabdomyolysis can occur with use of statins, causing acute kidney failure. The risk increases when statins are prescribed in combination with fibrates, nicotinic acid, calcineurin inhibitors (cyclosporin [Neoral], tacrolimus [Prograf]), erythromycin and azole antifungal agents.

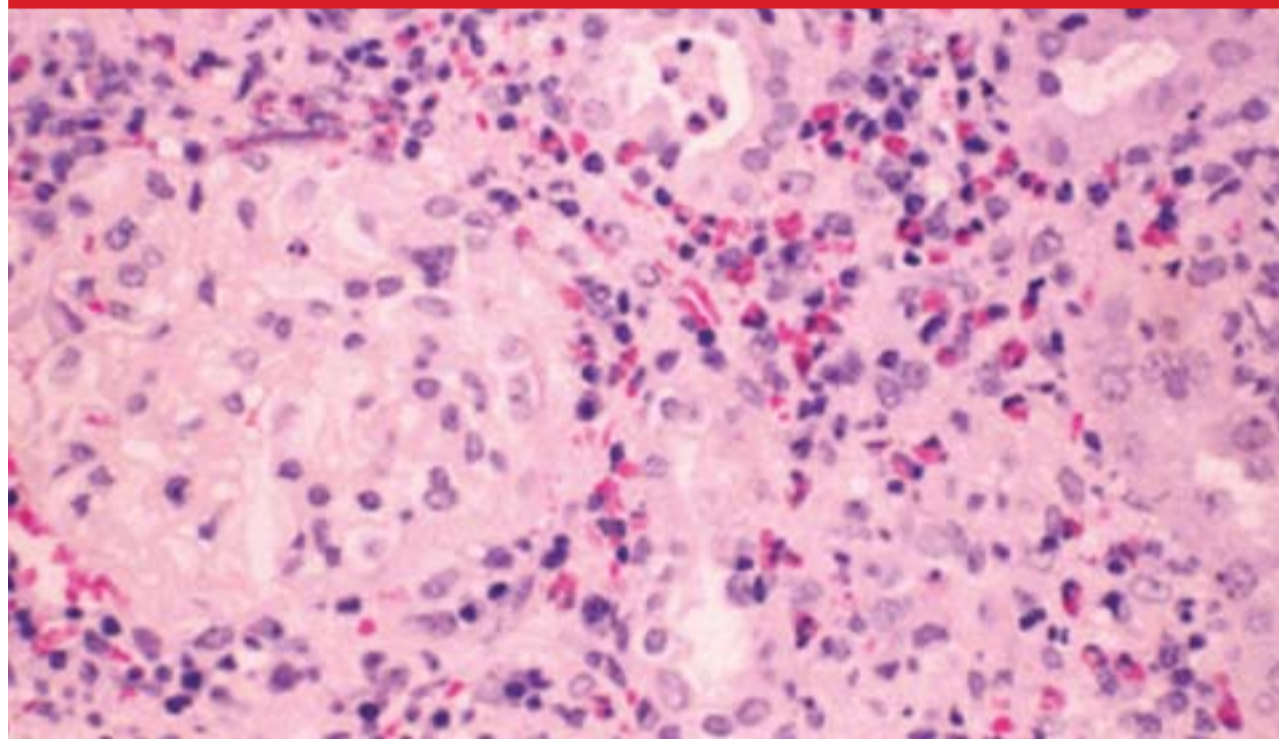
The Cardiac Society of Australia and New Zealand *Lipid Management Guidelines 2001*<sup>5</sup> recommend monitoring the levels of creatine kinase and liver enzymes in patients taking statins in combination with fibrates within the first six weeks of treatment, then at six-monthly intervals.

Chronic tubulo-interstitial nephritis can be caused by a

**Figure 3: Nephrotoxic agents that can cause acute kidney failure.**  
(Modified from Johnson J, Feehally J.<sup>4</sup> Reproduced with permission from Elsevier Ltd.)



**Figure 4: Acute allergic tubulo-interstitial nephritis.**



**Figure 5: Crystal-induced nephropathy due to indinavir (Crixivan)**



variety of drugs, including lithium carbonate (which also causes nephrogenic diabetes insipidus in 30-40% of patients). Many kidney dialysis units have at least one patient with end-stage kidney disease caused by lithium carbonate.

The risk of chronic tubulo-interstitial nephritis appears to

be related to the number of episodes of acute lithium toxicity and the duration of treatment, but there are no definite recommendations to guide management of patients with deteriorating kidney function in the context of long-term lithium therapy.

It is prudent to monitor

eGFR at least annually and to consider percutaneous renal biopsy in patients in whom the eGFR is falling. The decision to discontinue this effective drug needs to be made in consultation with the treating psychiatrist, while bearing in mind the risk:benefit ratio.

Other mechanisms of drug-induced kidney disease are more obscure. Various forms of drug-induced glomerulonephritis can occur but are rare. So called 'slow acetylators' are at increased risk of drug-induced lupus nephritis if challenged with drugs such as hydralazine (Alphapress, Apresoline), methyldopa (Aldomet, Hydopa), procainamide (Pronestyl), isoniazid, minocycline (Akamin, Minomycin) and propylthiouracil.

When drug related, crystal-induced nephropathy almost uniquely affects dehydrated patients with pre-existing kidney disease in whom the dose of a particular drug has not been appropriately adjusted to the GFR.

The most commonly implicated drugs are indinavir (Crixivan) (figure 5) and aciclovir, and this condition is most often encountered in practices specialising in HIV medicine. Ensuring appropriate dose adjustment and adequate fluid intake is crucial in these circumstances.

Special note should be made of acute kidney failure induced by parenteral bisphosphonates such as pamidronate (Aredia, Pamisol) and zoledronic acid (Zometa). About 10-15% of

patients receiving zoledronic acid in oncology clinics develop 'toxic' acute tubular necrosis secondary to proximal tubular toxicity.

Guidelines on the use of these drugs have recently been published<sup>6</sup> and recommend:

- A plasma creatinine mea-

surement should be obtained within 7-10 days before the first infusion of zoledronic acid.

- Plasma creatinine measurements should be obtained before each subsequent dose of zoledronic acid.
- Therapy should be tem-

porarily interrupted if plasma creatinine concentrations increase to twice the baseline or if an increase of 50µmol/L occurs in patients in whom the previous baseline measurement is less than 220µmol/L.

- Bisphosphonate therapy

should be discontinued if the plasma creatinine elevations do not resolve within 4-8 weeks.

Oral bisphosphonates are a safe alternative.

The incidence of thrombotic microangiopathy induced by clopidogrel

(Iscover, Plavix) is estimated to be 1.1-27.8 per million patients treated, but this drug is used commonly in Australia. It should be considered when acute kidney failure and thrombocytopenia (anaemia) occur together.

**Table 2: Drugs responsible for renal complications**

Drug class	Common examples	Renal complication	Mechanisms	Risk factors
Conventional NSAIDs*	Ibuprofen, naproxen, diclofenac sodium, indomethacin, ketoprofen, ketorolac, mefenamic acid, piroxicam, sulindac, tiaprofenic acid, tenoxicam	Acute kidney failure, sodium and water retention, hyponatraemia, hyperkalaemia, minimal-change glomerulonephritis, papillary necrosis	<ul style="list-style-type: none"> <li>■ Haemodynamically mediated reduction in GFR</li> <li>■ Acute allergic tubulo-interstitial nephritis</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, dose related, concurrent use of ACE inhibitor or angiotensin-II-receptor antagonist (ARA)
COX-2-selective NSAIDs*	Celecoxib, rofecoxib (no longer available), meloxicam	Acute kidney failure, sodium and water retention, hyponatraemia, hyperkalaemia	<ul style="list-style-type: none"> <li>■ Haemodynamically mediated reduction in GFR</li> <li>■ Acute allergic tubulo-interstitial nephritis</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, dose related, concurrent use of ACE inhibitor or ARA
ACE inhibitors*	Captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril	Acute kidney failure, hyperkalaemia	<ul style="list-style-type: none"> <li>■ Haemodynamically mediated reduction in GFR</li> <li>■ 'Ischaemic' acute tubular necrosis secondary to hypotension</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, atherosclerotic renal artery stenosis or fibromuscular dysplasia, concurrent use of conventional NSAID or COX-2 inhibitor
Angiotensin-II-receptor antagonists*	Candesartan, eprosartan, irbesartan, losartan, telmisartan	Acute kidney failure, hyperkalaemia	<ul style="list-style-type: none"> <li>■ Haemodynamically mediated reduction in GFR</li> <li>■ Ischaemic acute tubular necrosis secondary to hypotension</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, atherosclerotic renal artery stenosis or fibromuscular dysplasia, concurrent use of conventional NSAID or COX-2 inhibitor
Aminoglycosides*	Amikacin, gentamicin, neomycin, tobramycin	Non-oliguric acute kidney failure, hypomagnesaemia	<ul style="list-style-type: none"> <li>■ 'Toxic' acute tubular necrosis secondary to proximal renal tubule accumulation by endocytosis</li> <li>■ Renal tubular effects</li> </ul>	Divided daily dosing, greater age, chronic kidney disease, hypotension, sepsis, dehydration, concurrent liver disease, dose related
Antibiotics	Penicillins, rifampicin, cephalosporins, quinolones, sulfamethoxazole	Acute kidney failure	<ul style="list-style-type: none"> <li>■ Acute allergic tubulo-interstitial nephritis</li> <li>■ Intratubular crystal accumulation<sup>†</sup> (sulfonamides)</li> </ul>	Idiopathic
Antiviral agents	Aciclovir, famciclovir, indinavir	Acute kidney failure	Intratubular crystal accumulation <sup>†</sup>	Dehydration, rate of infusion, dose related
HMG-CoA reductase inhibitors (statins)	Atorvastatin, fluvastatin, pravastatin, simvastatin	Acute kidney failure	Pigment-induced nephropathy secondary to rhabdomyolysis	Concurrent use of fibrates or calcineurin inhibitors
Fibrates	Fenofibrate, gemfibrozil	Acute kidney failure	Pigment-induced nephropathy secondary to rhabdomyolysis	Concurrent use of fibrates or calcineurin inhibitors
Proton-pump inhibitors	Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Acute kidney failure and/or chronic kidney disease	Acute (or chronic) allergic tubulo-interstitial nephritis	Idiopathic
Calcineurin inhibitors*	Cyclosporin, tacrolimus	Acute kidney failure, chronic kidney disease, hyperkalaemia, hypomagnesaemia	<ul style="list-style-type: none"> <li>■ Haemodynamically mediated reduction in GFR</li> <li>■ Chronic tubulo-interstitial nephritis</li> <li>■ Thrombotic microangiopathy</li> <li>■ Pigment-induced nephropathy secondary to rhabdomyolysis</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, dose related, concurrent use of fibrates or statins
Loop-blocking diuretics*	Bumetanide, ethacrynic acid, frusemide	Acute kidney failure, hypokalaemia	<ul style="list-style-type: none"> <li>■ Acute ischaemic tubular necrosis secondary to dehydration</li> <li>■ Acute allergic tubulo-interstitial nephritis</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, dose related
Thiazide diuretics*	Chlorthalidone, hydrochlorothiazide	Acute kidney failure, hypokalaemia	<ul style="list-style-type: none"> <li>■ Acute ischaemic tubular necrosis secondary to dehydration</li> <li>■ Acute allergic tubulo-interstitial nephritis</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, dose related
Potassium-sparing diuretics*	Amiloride, spironolactone, triamterene	Acute kidney failure, hyperkalaemia	<ul style="list-style-type: none"> <li>■ Acute ischaemic tubular necrosis secondary to dehydration</li> <li>■ Acute allergic tubulo-interstitial nephritis</li> <li>■ Intratubular crystal accumulation<sup>†</sup> (triamterene only)</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, concurrent use of ACE inhibitor or ARA
Non-thiazide indole derivative of chlorosulfonamide*	Indapamide	Hyponatraemia, hyperkalaemia	Renal tubular effects	Idiopathic
Lithium carbonate*	Lithium carbonate	Acute kidney failure, chronic kidney disease	<ul style="list-style-type: none"> <li>■ Dehydration secondary to diabetes insipidus</li> <li>■ Chronic tubulo-interstitial nephritis</li> </ul>	Idiopathic, dose related
Cytotoxic antineoplastic chemotherapeutic agents	Multiple agents	Acute kidney failure	'Tumour lysis syndrome'	Dehydration, failure to prehydrate or premedicate with allopurinol
Platinum alkylating chemotherapeutic agent	Cisplatin	Acute kidney failure, severe hypomagnesaemia	<ul style="list-style-type: none"> <li>■ 'Toxic' acute tubular necrosis secondary to proximal and distal tubular toxicity</li> <li>■ Renal tubular effects</li> </ul>	Dehydration, dose related
Bisphosphonates*	Pamidronate, zoledronic acid	Acute kidney failure	<ul style="list-style-type: none"> <li>■ 'Toxic' acute tubular necrosis secondary to proximal tubular toxicity</li> <li>■ Focal segmental glomerulosclerosis</li> </ul>	Dehydration, dose related
Acute antigout agent <sup>†</sup>	Colchicine	Acute kidney failure	Pigment-induced nephropathy secondary to rhabdomyolysis	Idiopathic
Disease-modifying anti-rheumatic drugs <sup>†</sup>	Methotrexate Gold salts D-penicillamine	Acute kidney failure Nephrotic syndrome Nephrotic syndrome	Intratubular crystal accumulation <sup>†</sup> Membranous glomerulonephritis Minimal-change glomerulonephritis	Dehydration, dose related Idiopathic Idiopathic
Platelet adenosine diphosphate inhibitors <sup>†</sup>	Clopidogrel and ticlopidine	Acute kidney failure	Thrombotic microangiopathy	Idiopathic
Vitamin-K-dependent anti-coagulant <sup>†</sup>	Warfarin	Acute kidney failure	Spontaneous cholesterol athero-embolisation	Idiopathic

\*Common, †Rare, ††e, †††crystal-induced nephropathy

## Authors' case studies

### The 'triple whammy'

RD, a 72-year-old plumber, presented to his family physician with a one-day history of a red, hot, swollen left first metatarsophalangeal joint, and a background of ischaemic heart disease, hypertension and diet-controlled type 2 diabetes.

He had previously experienced numerous similar episodes. He had smoked a pack of cigarettes a day for 35 years but had stopped smoking 10 years ago. He admitted to drinking 14 units of alcohol a week. His medications included metoprolol 25mg bd, ramipril (Ramace, Tritace) 10mg at night, aspirin EC 100mg daily and frusemide 40mg in the morning.

On examination he was afebrile and haemodynamically stable. The affected joint was red, hot, swollen and tender. There was no evidence of arthritis involving any other joints and no skin rash. He had mild bilateral pitting oedema, but his cardiovascular examination was otherwise unremarkable.

The clinical diagnosis was gout. He was given dietary advice and started on indomethacin (Arthrexin, Indocid) 50mg tds with food.

Three days later, RD returned with worsening peripheral oedema and increasing shortness of breath. His examination was consistent with congestive cardiac failure. His foot was less swollen and he was now able to bear weight with only mild discomfort. His frusemide dose was doubled and follow-up arranged for one week.

Four days later RD presented with malaise, nausea, thirst and lightheadedness. He looked unwell and dehydrated. He had a tachycardia of 105 bpm and his blood pressure was 108/80mmHg, with a postural drop to 90/60mmHg. Auscultation of his chest was clear and the peripheral signs of congestive cardiac failure had resolved.

A blood test revealed a plasma creatinine concentration of 271µmol/L, increased from 117µmol/L one month before.

### Interpretation

RD has multiple risk factors for pre-existing kidney disease — older age, hypertension, diabetes, recurrent gout and documented ischaemic heart disease (vasculopathy increases the risk of renovascular disease).

His baseline plasma creatinine concentration was 117µmol/L which conferred an eGFR of 57mL/min/1.73m<sup>2</sup> using the MDRD formula, that is, despite his 'almost normal' plasma creatinine



**Specific clinical settings in which eGFR is not appropriate for use and GFR should be measured directly include ... extremes of body size and age.**

concentration, he already had stage-3 chronic kidney disease.

His ischaemic heart disease and hypertension were appropriately treated with an ACE inhibitor, beta blocker and aspirin, all of which have been shown to reduce morbidity and mortality in this patient group.

The addition of an NSAID led to fluid retention and reduced GFR. The subsequent increase in the dose of frusemide led to dehydration and pre-renal acute kidney failure.

The concurrent use of an ACE inhibitor, aspirin and NSAID compounded this by inhibiting the normal renoprotective compensatory autoregulatory mechanisms that normally preserve GFR (see Normal renal autoregulation and figure 2, p31).

This case illustrates some of the protective mechanisms the kidney employs to maintain GFR and how blocking these mechanisms can be a 'double edged sword'. Awareness of the potential for kidney failure, and knowledge of strategies to minimise this risk, play an important role in the management of patients with underlying chronic kidney disease.

Although in this case NSAIDs were effective in treating an attack of acute gout, strategies that may have reduced the risk of acute kidney failure included withholding the ACE inhibitor for 3-5 days during NSAID treatment and using alternative medications such as colchicine and/or corticosteroids to treat the acute gout before starting allopurinol (Allopurinol-BC, Allosig, Progot, Zyloprim) therapy at a later date.

### The pitfalls of eGFR

JW, 89, had recurrent severe normochromic normocytic anaemia requiring repeated hospital admission for blood

transfusions.

Her blood film, vitamin B<sup>12</sup> level and folic acid level were normal. Iron studies were consistent with anaemia of chronic disease. Her plasma creatinine was 75µmol/L (normal range 40-110µmol/L). Three stool samples for faecal occult blood were negative.

Gastroscopy and colonoscopy had been normal 18 months before and were not repeated, in view of her age and comorbidities.

Physical examination revealed a well but frail woman who was independent in all activities of daily living and weighed 35kg. Besides a marked dorsal kyphosis, physical examination was unremarkable.

### Interpretation

JW's eGFR, based on the modified MDRD equation, was reported as "eGFR >60mL/min/1.73m<sup>2</sup>". However, using the Cockcroft-Gault equation, her estimated creatinine clearance approximated to 24.85mL/min/1.73m<sup>2</sup>. A subsequent 24-hour collection of urine for protein and creatinine clearance (volume 3.4L) revealed 0.2g/day proteinuria and a creatinine clearance of 26mL/min/1.73m<sup>2</sup>, consistent with stage-4 chronic kidney disease.

The recent position statement published by the Australasian Creatinine Consensus Working Group states: "Specific clinical settings in which eGFR is not appropriate for use and GFR should be measured directly include ... extremes of body size and age". This is particularly relevant in the case of frail elderly women.

Based on these measurements, anaemia of chronic disease secondary to stage-4 chronic kidney disease was diagnosed. JW was administered an iron infusion and started on darbepoetin

(Aranesp) 20g subcutaneously weekly. Her haemoglobin has stayed between 110 and 120g/L and she has not required hospital admission or blood transfusion for more than six months.

### Great for mental health ... not so hot for the kidney!

CR presented to her GP for repeat prescriptions. She also complained of increasing lethargy and malaise. Her clinical history included hypertension, hyperlipidaemia and bipolar affective disorder. She had suffered no manic or depressive episodes for over eight years and her physical examination was unremarkable.

She had been taking eprosartan/hydrochlorothiazide (Teveten plus) 600/12.5mg daily and simvastatin 20mg at night for five years, and lithium carbonate (Lithicarb, Quilonum SR) 250mg in the morning and 500mg at night for 11 years. She experienced mild lithium-induced diabetes insipidus which she tolerated by drinking large volumes of water.

Initial investigations revealed normal FBC, liver function tests, TSH and C-reactive protein. The serum urea and creatinine were elevated at 9.2mmol/L and 123µmol/L (99µmol/L two years before), respectively.

Other blood and urine tests were unremarkable apart from a 24-hour collection of urine showing a creatinine clearance of 53mL/min/1.73m<sup>2</sup> (normal range 60-200mL/min/1.73m<sup>2</sup>) and 0.46mg/day protein (normal range 0.0-0.14mg/day). A nuclear medicine 99mTc-DTPA scan confirmed a reduced creatinine clearance of 48.6mL/min/1.73m<sup>2</sup> consistent with stage-3 chronic kidney disease. Renal tract ultrasound showed shrunken

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## References

1. National Kidney Foundation. Kidney Disease Outcomes Quality Initiative (KDOQI). Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *American Journal of Kidney Disease* 2002; 39[2 Suppl.1]:S1-S266. Available at: [www.kidney.org/professionals/kdoqi/guidelines.cfm](http://www.kidney.org/professionals/kdoqi/guidelines.cfm) (accessed March 2006).
2. Levey AS, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine* 1999; 130:461-70.
3. Thadhani R, et al. Acute renal failure *New England Journal of Medicine* 1996; 334:1448-60.
4. Johnson J, Feehally J. *Comprehensive Clinical Nephrology*. 2nd edn. Mosby, 2003.
5. National Heart Foundation of Australia and The Cardiac Society of Australia and New Zealand. Lipid Management Guidelines 2001. *Medical Journal of Australia* 2001; 175:S57-S88. [www.mja.com.au/public/guides/guides.html](http://www.mja.com.au/public/guides/guides.html) (accessed March 2006).
6. Berenson JR. Recommendations for zoledronic acid treatment of patients with bone metastases. *The Oncologist* 2005; 10:52-62.

## Online resources

- Renal Resource Center: [www.renalresource.com](http://www.renalresource.com)
- Kidney Health Australia: [www.kidney.org.au](http://www.kidney.org.au)
- National Prescribing Service Limited: [www.nps.org.au](http://www.nps.org.au)
- The Clinical Information Access Program: [www.ciap.health.nsw.gov.au](http://www.ciap.health.nsw.gov.au)

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kidneys (8.8cm on the right and 8.9cm on the left) with increased echogenicity consistent with chronic disease.

In the absence of any other aetiological factors predisposing to chronic kidney disease, a diagnosis of chronic lithium-induced nephropathy was made. The treating psychiatrist was consulted and sodium valproate (Epilim, Valpro) 300mg twice daily introduced while the patient's lithium carbonate dose was weaned to zero over several months. Seventeen months later the patient was well and her chronic kidney disease was stable.

#### Interpretation

Though very effective in the treatment of bipolar affective disorder, lithium carbonate causes diabetes insipidus, which may occur soon after initiating therapy of varying severity in up to a third of patients.

Unrelated to this, chronic lithium carbonate therapy can lead to chronic interstitial nephritis. Percutaneous renal



biopsy was not performed because the diagnosis was considered probable and the risk of renal biopsy in a patient with shrunken kidneys (however small) was consid-

ered unjustified and unlikely to change management.

#### Gym-junkie

JC, 21, presented to his GP for review and blood tests

because of a two year history of unexplained lethargy. He was otherwise healthy and active, attending the gym for 90 minutes 4-5 times per week. He denied ever taking any recreational drugs. He was taking no prescription medications but admitted to taking vitamin and creatine supplements purchased at his gym. Physical examination revealed a fit looking, muscular athlete with no abnormal findings.

Blood tests unexpectedly revealed a raised serum creatinine of 130µmol/L. The patient had no identifiable risk factors predisposing to renal disease. Extensive tests including a 24-hour collection of urine for protein and creatinine clearance and renal tract ultrasound were also normal.

It was considered likely that the raised serum creatinine was due to ingestion of up to 3g of creatine supplements daily combined with relative dehydration induced by very hot weather and an inadequate fluid intake. The patient was encouraged to

reduce the amount of creatine he was taking and to drink at least 2.5L fluid per day. All subsequent blood and urine tests were well within normal limits.

#### Interpretation

Creatine is a popular supplement used by athletes in an effort to increase muscle performance. Creatine supplementation appears safe when used by healthy adults at the recommended loading (20g/day for five days) and maintenance doses (≤3g/day). In people with a history of kidney disease or those taking nephrotoxic medications, creatine may be associated with an increased risk of kidney dysfunction. There are case reports of acute kidney failure associated with the ingestion of quantities of creatine in excess of the above guidelines. Since creatine supplementation may increase creatinine levels, it may act as a false indicator of renal dysfunction, as above. Enquiring about non-prescription medications can be important.



## How To Treat Quiz

Kidney complications of commonly used drugs – part 1 — 7 April 2006

#### INSTRUCTIONS

Complete this quiz to earn 2 CPD points and/or 1 PDP point by marking the correct answer(s) with an X on this form. Fill in your contact details and return to us by fax or free post.

#### FAX BACK

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#### FREE POST

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#### ONLINE

[www.australiandoctor.com.au/cpd/](http://www.australiandoctor.com.au/cpd/) for immediate feedback

#### 1. In which THREE ways are drugs likely to influence kidney function?

- a) By drug interactions
- b) Through potentially life-threatening allergic reactions
- c) By impairing normal autoregulatory mechanisms that protect kidney blood flow
- d) By direct toxicity to the renal tubules

#### 2. Which TWO statements about the relationship between the GFR, estimated glomerular filtration rate (eGFR), plasma creatinine and acute kidney failure are correct?

- a) Acute kidney failure can be defined as an abrupt rise in plasma creatinine concentration of >50µmol/L in a patient with a previous baseline measurement of <220µmol/L
- b) GFR must fall by about 20% below the normal range before plasma creatinine concentration rises outside the normal range
- c) eGFR measurements are equally reliable in detecting chronic kidney diseases in people of all races
- d) A relatively small decline in GFR in patients with pre-existing chronic kidney disease may lead to a large increase in plasma creatinine concentration

#### 3. Which TWO test findings are consistent with a diagnosis of chronic kidney disease?

- a) Urine albumin:creatinine ratio >3.4mg/mmol on two spot urine tests

- b) Scarring on renal imaging
- c) Plasma creatinine >110µmol/L in all cases
- d) Glycosuria

#### 4. Stefano, 57 and a new patient, has increasing breathlessness. His BMI is 31 and he has elevated blood pressure. His only medication is a thiazide diuretic. Stefano has a GFR of 95mL/min/1.73m<sup>2</sup> and test findings consistent with chronic kidney disease. Which TWO conclusions can you draw about his level of kidney dysfunction?

- a) Stefano has stage 1 chronic kidney disease
- b) The cause of his chronic kidney disease is not important at this stage
- c) Regular monitoring of his kidney function is required
- d) At this level of GFR he is not at risk of potential kidney complications caused by medications

#### 5. Which TWO comorbidities would be most likely to increase his risk of acute-on-chronic kidney failure?

- a) Parkinson's disease
- b) Diabetes
- c) Severe heart failure
- d) Hyperlipidaemia

#### 6. Stefano's wife calls for a home visit. He has back pain after an injury and has

#### been taking ibuprofen at high doses for three days. His blood pressure is 100/60mmHg lying and he has a postural drop. Which TWO actions are you most likely to take?

- a) Change his ibuprofen to a COX-2 inhibitor
- b) Start rehydration
- c) Continue his diuretic
- d) Arrange for urgent measurement of his plasma creatinine and GFR

#### 7. Stefano recovers and returns for review a week later. His GFR is now 57mL/min/1.73m<sup>2</sup> and his blood pressure (on no treatment) is 150/95mmHg. He has mild ankle oedema but no other signs of heart failure. Which THREE actions are you most likely to take?

- a) Introduce a loop diuretic rather than a thiazide to control his oedema, because it is less likely to cause acute kidney failure
- b) Emphasise the importance of blood pressure control
- c) Refer to a nephrologist
- d) Advise Stefano to avoid all types of NSAIDs in the future

#### 8. Mietta, 53, has elevated total and LDL-cholesterol levels and raised triglycerides. Her sister had an MI at the age of 46. Mietta's plasma creatinine and eGFR are in the normal range. You discuss diet and treatment with a statin. Which warnings

#### would you give Mietta (choose TWO)?

- a) Significant myositis occurs in 5% of patients taking statins
- b) Taking erythromycin with a statin increases her risk of acute kidney failure
- c) She should see you if she develops any muscle tenderness or pain
- d) Topical antifungal agents should be avoided

#### 9. Mietta's cholesterol levels have improved but her triglycerides remain elevated and you discuss adding a fibrate. How would this change Mietta's risk of rhabdomyolysis and what monitoring would you advise if she has no symptoms when the drug is introduced (choose ONE)?

- a) Her risk of rhabdomyolysis is unchanged
- b) Monitor creatinine at monthly intervals
- c) No routine monitoring is needed if her eGFR is normal
- d) Measure levels of creatine kinase and liver enzymes within the first six weeks of treatment, then at six-monthly intervals

#### 10. Which TWO drugs are known to cause chronic tubulo-interstitial nephritis?

- a) Colchicine
- b) Lithium carbonate
- c) Proton-pump inhibitors
- d) Warfarin

#### CONTACT DETAILS

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RACGP QA & CPD No: ..... and/or ACRRM membership No: .....

Address: ..... Postcode: .....

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer. Your CPD activity will be updated on your RACGP records every January, April, July and October.

**NEXT WEEK** Kidney complications of drugs concludes next week with guidance on prescribing drugs for patients with impaired kidney function, including renin-angiotensin inhibition in chronic kidney disease; advice about radiocontrast-induced nephropathy; and what to do if you suspect drug-induced kidney failure.

Australian Doctor  
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