



# Prescribing in renal disease

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## Summary

The appropriate prescribing of many drugs depends on knowledge of the patient's total renal function, which is proportional to their body mass. The Cockcroft-Gault method of calculating creatinine clearance takes into account the patient's weight. The recently introduced estimated glomerular filtration rate, which is now routinely reported with biochemistry test results, is useful for screening for renal disease, but is unsuitable for calculating doses as it does not take into account the patient's size. Both are unreliable at extremes of weight. The list of medications that need dosage adjustment according to renal function is long, but includes commonly prescribed drugs such as antivirals, hypoglycaemic drugs (metformin, sulfonylureas, insulin), spironolactone and allopurinol.

Key words: creatinine clearance, drug therapy, glomerular filtration rate, kidney disease.

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## Introduction

The clearance of many drugs and their metabolites depends on adequate renal function. Renal clearance is especially important for some drugs where the gap between efficacy and toxicity is narrow. Doses of these drugs need careful adjustment if they are prescribed for patients with impaired renal function. Some drugs also have the potential to cause renal toxicity. This is particularly likely to occur in patients who already have some degree of renal impairment, although other factors can increase the risk.

## Estimating renal function

An accurate estimation of renal function, or glomerular filtration rate (GFR), requires sophisticated techniques that are unsuitable for routine or repeated use. In practice, the serum creatinine concentration is used for day-to-day assessment of renal function. It has limitations, but it remains a robust and practical parameter for most clinical situations.

## Serum creatinine

The serum creatinine concentration has important limitations when used for estimating renal function.

1. There is an inverse relationship between serum creatinine and renal function. A doubling of serum creatinine represents a halving of GFR. A person's serum creatinine can rise from 60 to 120 micromol/L and so still be in the normal range (typically 50 to 120 micromol/L), yet the renal function has deteriorated dramatically.
2. Renal function declines steadily with age in adults, but this is not reflected in the serum creatinine, which remains steady or may only increase slightly with age (in the absence of overt renal disease, where it may rise more obviously). An 80-year-old will have approximately half of the renal function of a 20-year-old, despite both having the same serum creatinine concentration.
3. Renal function has an approximately linear relationship with lean body mass. In the presence of the same serum creatinine, a 120 kg person will have twice the renal function of a 60 kg person because they have bigger kidneys.
4. Women have a lower muscle mass than men of equivalent weight and age. A woman's serum creatinine represents approximately 0.85 of the renal function of a man with the same serum creatinine.

These limitations are particularly relevant and must be addressed when attempting to measure renal function for the purpose of calculating drug doses.

## Creatinine clearance

The serum creatinine concentration represents a balance between its production in the body (from muscle) and its excretion by the kidneys. From this can be derived an estimation of the creatinine clearance by the kidneys, in millilitres per minute (mL/min) or millilitres per second (mL/sec). This is the notional volume of serum that is cleared of creatinine in those times. The creatinine clearance is the 'poor man's' equivalent of the formal measurements of GFR, but for most clinical purposes is an adequate measurement of renal function.

Direct determination of creatinine clearance requires simultaneous measurement of the concentration of creatinine in the serum and in a timed urine specimen (usually 24 hours).

Timed urine collections are labour-intensive and notoriously unreliable. As a result many equations for estimating creatinine clearance have been derived that only need measurement of serum creatinine. The most widely recognised of these is the Cockcroft-Gault formula, which relies on patient age, weight, gender and serum creatinine.

$$\text{creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{lean body weight (kg)} \times (0.85 \text{ for females})}{\text{serum creatinine (micromol/L)} \times 0.815}$$

The accuracy of this formula for estimating creatinine clearance is equivalent to that from a timed urine collection, so there is no good reason for using a 24-hour collection. Manufacturers' renal dosing recommendations for medications are based on Cockcroft-Gault estimates of renal function, so this formula is also recommended when estimating creatinine clearance for the purpose of calculating drug doses that vary according to renal function.

Clinicians should be aware of some important limitations of the Cockcroft-Gault estimation of renal function. It is:

- not validated in some populations
- unreliable in extremes of body size (that is, in severe malnutrition or obesity)
- imprecise and unreliable for rapidly changing renal function (for example intensive care, acute renal failure).

## What is estimated GFR?

Australian pathology laboratories have started routinely including an estimated GFR (eGFR) in all biochemistry reports that include serum creatinine. The reporting of serum creatinine has also been standardised to be in micromol/L (so the actual number is 1000 times that when reported as mmol/L).

The formula used to calculate eGFR was derived as part of a large study of the effect of dietary protein restriction on the progression of renal failure. (This was the Modification of Diet in Renal Disease study, hence the MDRD formula.<sup>1</sup>) The advantage of this formula is that it does not require knowledge of the patient's height or weight as the eGFR is calculated using serum creatinine, age and gender.

It is crucial that clinicians realise that the eGFR is not estimating the patient's **actual** GFR, but is estimating an **adjusted** GFR – which assumes that the patient is of average body size. This explains how the number can be calculated without any knowledge of the patient's actual size. Average body size equates to a body surface area of 1.73 m<sup>2</sup>, and so the eGFR is reported as mL/min/1.73 m<sup>2</sup>. In practice, this means that while one person who is twice the size of another, of the same age, gender and serum creatinine, will have twice the actual GFR, the eGFR for both will be the same.

The eGFR is primarily intended to be a screening tool for renal disease in the community, in association with other signs of

renal disease such as urinary abnormalities and hypertension. It has similar limitations as the Cockcroft-Gault equation<sup>2</sup>, including that it is not validated in Aboriginal and Torres Strait Islander people.

## eGFR is not preferred for calculating drug doses

Drug dosing should be based on the patient's actual GFR and not an adjusted GFR. While recognising that the Cockcroft-Gault equation has limitations, it does at least take into account body size when estimating GFR, whereas the eGFR does not. Using the eGFR to calculate dosages would lead to overdosing of small patients and underdosing of large patients. Overdosing increases the risk of toxicity of drugs with a narrow therapeutic range, while underdosing reduces efficacy. The MDRD formula used to calculate eGFR can be manipulated to adjust for a patient's body surface area (if the patient's height and weight are known). A recently published observational analysis suggests wide variation between the formulas.<sup>3</sup> However, as yet it is unknown whether the MDRD formula is superior to Cockcroft-Gault for calculating drug doses.

## Prescribing for dialysis patients

For the purpose of drug prescribing, patients on dialysis (haemodialysis or peritoneal dialysis) should be considered to have a creatinine clearance/GFR of less than 10 mL/min. Certain drugs are actively removed from the circulation during dialysis, and this needs to be considered when deciding on the timing of administration as well as the dosage. Factors that may reduce the extent to which a drug is dialysed include large molecular size of the drug, high protein binding, large volume of distribution and high lipid solubility. In addition to these parameters, the type of dialyser membrane may also affect drug clearance, as will blood and dialysate flow rates. If a drug is known to be dialysed, patients having haemodialysis may be instructed to take the drug after the dialysis session.

## Dose alteration in renal impairment

Once renal impairment has been detected and creatinine clearance estimated, the need for dose alteration of renally cleared drugs must be determined. Generally dose adjustment is needed when the creatinine clearance is below 60 mL/min. People who have been taking a drug for many years may need a dose adjustment as they age. Adjustments can be achieved by a reduction in dose, or an extension of the dosing interval, or both. Knowledge of appropriate dosage adjustment is important to ensure the drug is effective and that accumulation and further kidney damage is avoided. There are various references to consult in Australia including the approved product information and the Australian Medicines Handbook. International references include the Renal Drug Handbook and Drug prescribing in renal failure.<sup>4</sup> Table 1 lists some of the commonly prescribed drugs that require dose alteration in renal impairment.

Table 1

**Commonly prescribed drugs that require dose adjustment in renal impairment**

Class	Examples
Antibiotics/antifungals	aminoglycosides (e.g. gentamicin), vancomycin, ceftazidime, cefepime, cephalosporins, ciprofloxacin, fluconazole, piperacillin, carbapenems (e.g. meropenem), sulfamethoxazole
Antivirals	famciclovir, aciclovir, valaciclovir, valganciclovir, ganciclovir
Anticoagulants	low molecular weight heparins (e.g. enoxaparin)
Cardiac drugs	digoxin, sotalol, atenolol
Diuretics	If creatinine clearance is less than 30 mL/min: <ul style="list-style-type: none"> <li>- avoid potassium-sparing diuretics due to risk of hyperkalaemia</li> <li>- thiazide diuretics have limited efficacy</li> </ul>
Opioids	morphine, codeine, pethidine (due to risk of accumulation of active or toxic metabolites)
Psychotropics/anticonvulsants	amisulpride, gabapentin, lithium, levetiracetam, topiramate, vigabatrin
Hypoglycaemic drugs	metformin, glibenclamide, glimepiride, insulin
Drugs for gout	allopurinol, colchicine
Others	lamivudine, methotrexate, penicillamine

**Antiviral drugs**

Renal clearance is the major route of elimination for many antivirals, including those used for treating herpes simplex, herpes zoster and cytomegalovirus infections (such as aciclovir, famciclovir, valganciclovir and ganciclovir). In patients with renal impairment, renal clearance of these drugs is reduced and the elimination half-life is significantly prolonged. As a result, normal doses will accumulate and may lead to neurological signs such as dizziness, confusion, hallucinations, somnolence and convulsions, as well as more rarely, tremor, ataxia, dysarthria, seizures and encephalopathy. These adverse effects are dose-related and reversible on stopping the drug. They are especially problematic in elderly patients or patients taking other neurotoxic medications. If essential, it may be possible to reintroduce the drug at a lower dose.

**Hypoglycaemic drugs**

Renal function needs to be considered when prescribing three of the major groups of hypoglycaemic drugs – biguanides (metformin), sulfonylureas and insulin.

**Metformin**

Metformin has been associated with rare but potentially fatal lactic acidosis. This is thought to result from accumulation of metformin when renal impairment reduces renal clearance. The risk of lactic acidosis is potentially enhanced in conditions where tissue hypoperfusion and hypoxaemia are a problem (for example in cardiac or respiratory failure, or following a

myocardial infarction), with increasing age and with higher doses of metformin (generally above 2 g/day). The common adverse effect of nausea is also dose-related and more likely to occur in the presence of renal impairment.

No definitive guidelines exist on reducing the dose of metformin in renal impairment, and lactic acidosis has been reported with doses as low as 500 mg/day.<sup>5</sup> Ideally, metformin should be avoided in patients with a creatinine clearance of less than 30 mL/min and should be used with caution, at a reduced maximum daily dose of 1 g, in patients with a creatinine clearance of 30–60 mL/min. For those patients with a creatinine clearance of 60–90 mL/min, the recommended maximum daily dose is 2 g. Metformin should also be withheld temporarily in patients undergoing surgery, suffering from dehydration, trauma or serious infections, or undergoing procedures likely to affect renal function (for example, contrast studies).

**Sulfonylureas**

Long-acting sulfonylureas such as glibenclamide and glimepiride are associated with a higher risk of hypoglycaemia in comparison to short-acting sulfonylureas. In patients with renal impairment and/or advanced age, the risk of hypoglycaemia is increased. These drugs are inherently long-acting as well as having metabolites that are excreted renally. Shorter-acting sulfonylureas such as gliclazide or glipizide are a safer choice in patients with renal impairment. They should be started at a low dose and increased gradually.

## Insulin

Renal elimination accounts for up to half of the clearance of insulin, so as renal failure progresses, less insulin is excreted, so smaller doses are required. Patients with diabetes and renal impairment can also have unrecognised gastroparesis which may disconnect absorption of ingested food from the time of the insulin injection. This can lead to erratic glucose regulation that may be complicated by frequent episodes of hypoglycaemia.

## Spirolactone

Since the publication of the Randomized Aldactone Evaluation Study<sup>6</sup> in 1999, the use of spironolactone, in conjunction with an angiotensin-converting enzyme (ACE) inhibitor, has increased. In this trial, the addition of spironolactone significantly improved morbidity and mortality in patients with advanced heart failure. However, almost immediately following this publication came reports of an increase in hospital admissions (and subsequent deaths) related to hyperkalaemia.<sup>7</sup>

Hyperkalaemia is a particular problem for patients with renal impairment and its risk is heightened by advanced age, doses of spironolactone exceeding 25 mg/day, dehydration, diabetes mellitus, and simultaneous treatment with non-steroidal anti-inflammatory drugs, ACE inhibitors or angiotensin receptor antagonists. Prescribers are urged to frequently monitor serum potassium, creatinine and urea when starting spironolactone for heart failure, and to consider avoiding its use in patients with a creatinine clearance of less than 30 mL/min.

## Allopurinol

Allopurinol is used in the management of gout to lower serum and urinary uric acid concentrations. As allopurinol, and its active principal metabolite oxypurinol, are mainly excreted in the urine, they accumulate in patients with poor renal function so the dose should be reduced. The manufacturers recommend starting treatment with a maximum dose of 100 mg/day and increasing it only if the serum or urinary urate is not satisfactorily controlled.

Hypersensitivity reactions to allopurinol are characterised by fever, chills, leucopenia, eosinophilia, arthralgia, rash, pruritis, nausea and vomiting. The frequency of this reaction is thought to be increased in patients with renal impairment, and in those who are concomitantly taking allopurinol and a thiazide diuretic. Caution is advised when using this combination in renal impairment.

## Conclusion

Adjusting the dose of renally cleared drugs is important when prescribing for patients with renal impairment. There are many drugs that require dose adjustment according to renal function. Estimation of creatinine clearance and hence renal function

can be determined using the Cockcroft-Gault equation. The role of the MDRD equation (expressed as eGFR on biochemistry reporting) is currently as a screening tool for kidney disease.

## References

1. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-70.
2. Mathew TH. The Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005;183:138-41.
3. Wargo KA, Eiland EH 3<sup>rd</sup>, Hamm W, English TM, Phillippe HM. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. *Ann Pharmacother* 2006;40:1248-53.
4. Aronoff GR, Berns JS, Brier ME, Golper TA, Morrison G, Singer I, et al. Drug prescribing in renal failure: dosing guidelines for adults. 4th ed. Philadelphia: American College of Physicians–American Society of Internal Medicine; 1999.
5. Nisbet JC, Sturtevant JM, Prins JB. Metformin and serious adverse effects. *Med J Aust* 2004;180:53-4.
6. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.
7. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;351:543-51.

## Further reading

Nankivell BJ. Creatinine clearance and the assessment of renal function. *Aust Prescr* 2001;24:15-7.

Johnson CA, Simmons WD. 2006 Dialysis of drugs. Wisconsin: Nephrology Pharmacy Associates; 2006. [http://www.nephrologypharmacy.com/pub\\_dialysis.html](http://www.nephrologypharmacy.com/pub_dialysis.html) [cited 2007 Jan]

Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function – measured and estimated glomerular filtration rate. *N Engl J Med* 2006;354:2473-83.

The Renal Drug Handbook. 2nd ed. Ashley C, Currie A, editors. Oxford: Radcliffe Medical Press; 2004.

*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page 27)*

3. Estimates of glomerular filtration rate are unreliable if the creatinine clearance is rapidly changing.
4. Renal impairment increases the risk of lactic acidosis in patients taking metformin.