# RENAL UPDATE

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***"Renal Impairment"***

# Action plan for Chronic Kidney Disease

## (*Based on eGFR)*

| **eGFR** mL/min/1.73 $m^2$ | **Description** | **Clinical action plan** |
|---|---|---|
| **≥ 60** | No kidney damage<br><br>OR<br>Stage 1 CKD<br>(Kidney damage with normal or ↑ kidney function) ± proteinuria<br><br>OR<br>Stage 2 CKD<br>(Kidney damage with mild ↓ kidney function) | Further investigation for CKD may be indicated in those at increased risk (smoking, diabetes, high blood pressure, age over 50 years, family history, Māori or Pacific Island or Asian heritage:<br>- Assessment of proteinuria<br>- Urinalysis<br>- Blood pressure<br><br>Cardiovascular risk reduction (blood pressure, lipids, blood glucose, smoking, obesity, physical activity)<br>Blood pressure targets ≤ 130/80; ≤ 122/76 if protein > 1 g/24 hours |
| **30 - 59** | Stage 3 CKD – Moderate ↓ kidney function | As for Stage 2 plus:<br>- Blood pressure control<br>- Monitor eGFR 3 monthly<br>- Avoid nephrotoxic drugs (e.g. NSAIDS, colchicine)<br>- Prescribe antiproteinuric drugs (ACE inhibitors and/or angiotensin receptor blockers) if appropriate<br>- Address anaemia, acidosis and hyperparathyroidism<br>- Ensure drug dosages appropriate for level of kidney function (adjust according to Cockcroft-Gault equation)<br><br>Consider referral to nephrologist |
| **15 - 29** | Stage 4 CKD – Severe ↓ kidney function | As for Stage 3 plus:<br>- Referral to nephrologist is usually indicated for preparation for dialysis (including access surgery, education) or transplantation |
| **< 15** | Stage 5 CKD – End-stage kidney failure | As for Stage 4 plus referral to nephrologist |

# Guide to drug dose adjustment in Renal Impairment

***(Based on Cockcroft-Gault equation, Adapted from BNF[1])***

| | **Degree of renal impairment as per GFR** |
|---|---|
| ***Drug or class of drug*** | ***Dose adjustment based on creatinine clearance*** |
| **Allopurinol** | 10–20 mL/min; 100–200 mg daily<br><10 ml/min; 100 mg on alternate days (max 100 mg daily) |
| **ACE inhibitors** | Start low and go slow. Start with very low doses and titrate to maximum tolerated dose. Proceed cautiously at doses above enalapril 10 mg or equivalent, i.e. captopril 75 mg or cilazapril 2.5 mg daily |
| **Bezafibrate 400 mg (Bezalip retard)** | < 60 mL/min; Avoid<br>(For 200 mg tablets see product data sheet) |
| **ß-blockers** | Dose reduction of some ß-blockers required, especially atenolol, sotalol and nadolol. Refer to individual drug datasheets |
| **Cotrimoxazole** | < 15 mL/min; Avoid<br>15–30 ml/min; Use half normal dose |
| **Colchicine**<br>**(from Prescriber Update, Nov 2005)** | < 10 mL/min; avoid<br>< 50 mL/min; reduce dose by half |
| **Digoxin** | Dose adjustment required in renal impairment (including age related). Adjust according to plasma concentrations |
| **Lithium** | Dose adjustment required in renal impairment (including age related). Adjust according to plasma concentrations |
| **Metformin***<br>**(from bpac$^{nz}$ Diabetes POEMs, Oct 2004)** | < 30 mL/min; avoid<br>30–60 mL/min; max 1000 mg/day<br>60–90 mL/min; max 2000 mg/day |
| **Nitrofurantoin** | Avoid in mild, moderate and severe impairment |
| **NSAIDs** | Mild impairment; Use lowest effective dose and monitor renal function, sodium and water retention<br>Moderate and Severe; avoid if possible |
| **Ranitidine** | < 20 mL/min; use half the normal dose |
| **Simvastatin** | < 30 mL/min; Doses above 10 mg daily should be used with caution |
| **Venlafaxine** | < 10 mL/min; avoid<br>10–30 mL/min; use half normal dose |

* Some references recommend avoiding metformin even in mild renal impairment but metformin can be used with caution if the dose is reduced. All patients should be advised to withhold treatment and seek medical advice if they experience vomiting and diarrhoea and if they have planned medical, surgical or radiological procedures.

Drugs that are excreted renally (or have renally excreted metabolites) generally require an adjustment in dose in people with renal impairment to avoid accumulation and potential toxicity. As the GFR also declines with age, smaller doses of renally excreted drugs may be required in the elderly. The magnitude of the adjustment is determined by the degree of renal impairment (reduction in GFR), and involves giving smaller doses at the same frequency or the same dose at an increased dosing interval.

Dose adjustment in people with renal impairment is conventionally achieved by dose modification corresponding to a value of creatinine clearance. Many tables and reference texts, including the BNF, list degrees of renal impairment (mild; moderate; severe) according to creatinine clearance and recommend a dose according to the degree of impairment.

***Degrees of renal impairment in relation to calculated creatinine clearance (BNF)***

| | |
|---|---|
| Severe | < 10 mL/min |
| Moderate | 10–20 mL/min |
| Mild | 20–50 mL/min |

Page 20 outlines an update of our "Common Sense" guide published in 2002. You may notice that the bands of creatinine clearance values for mild, moderate and severe impairment have changed slightly. This is in line with the ranges used by the BNF on which the information in the table is based.

# eGFR vs Cockcroft-Gault

## Why use different measures for grading chronic renal failure and adjusting drug doses?

The MDRD equation has not been validated to guide the adjustment of drug doses in renal impairment so use of the Cockcroft-Gault equation is still recommended.

While it is likely that in many cases when the eGFR is 60 mL/min or less that the calculated creatinine clearance will be very similar to the eGFR, differences could occur if the person has a body surface area significantly lower or higher than 1.73 $m^2$.

Drug dose adjustment is based on the actual GFR and the best way of calculating this remains the Cockcroft-Gault equation.

Alternatively some authors[4,5] have suggested that an eGFR value can be converted to an actual GFR as follows:

$$\text{Actual GFR} = \text{eGFR} \times \frac{\text{Actual body surface area}}{1.73\ m^2}$$

For the moment bpac recommends that the Cockcroft-Gault equation is used for drug dose adjustment until the above suggested correction has been fully validated. In practice, it would be worthwhile comparing the two methods, and we welcome feedback on your observations.

**Cockcroft-Gault equation for adjusting drug doses**

Serum creatinine itself is not a good marker of renal function and moderate renal dysfunction (early stages of Chronic Kidney Disease - CKD) can occur with serum creatinine values within the reference range.

Kidney function is determined by measurement of the Glomerular Filtration Rate (GFR). Direct determination of the GFR involves measurement of the renal clearance of inulin (a polysaccharide) or a radioactive compound. It is not usually practical to measure GFR directly so methods of estimating GFR have been developed. With some limitations, the renal clearance of creatinine (creatinine clearance) closely matches the GFR. Therefore the most widely used estimate has been the Cockcroft-Gault equation (Table 1) which computes an estimate of creatinine clearance from serum creatinine, age, gender and body weight.

***Table 1: Cockcroft-Gault equation for calculating creatinine clearance***

$$\text{Creatinine Clearance mL/min} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{815 \times \text{serum creatinine (mmol/L)}}$$

Multiply by 0.85 for females as they have a smaller muscle mass than males. As creatinine is derived from muscle it is more accurate to use Lean Body Weight but for practical purposes the actual body weight can be used except in significant obesity.

Creatinine clearance is a surrogate marker of the GFR but several variables can affect the accuracy of the estimate.

In severe renal impairment creatinine is actively secreted and the Cockcroft-Gault equation may over-estimate renal function. As creatinine originates from skeletal muscle its production can be influenced by muscle mass and the degree of physical activity. It is less accurate in those over 85 years and in people with a body mass significantly outside the normal range. It is not applicable in children.

From a practical perspective determination of creatinine clearance and estimation of renal function requires an active calculation step, using the patient's weight and in some cases estimation of Lean Body Weight.

**eGFR for detection of Chronic Kidney Disease**

eGFR is a relatively new method of estimating the GFR. It is calculated using the Modification of Diet in Renal Disease (MDRD) equation (Table 2) which uses four variables; age, serum creatinine, gender and ethnicity. This allows an eGFR to be calculated whenever a serum creatinine is ordered without details of the patient's weight. Most laboratories in New Zealand now automatically report eGFR whenever a serum creatinine is requested. This allows the practitioner to assess kidney function without having to estimate creatinine clearance using the Cockcroft-Gault equation. Provision of the eGFR allows an initial screen for chronic kidney disease and the possibility of early detection.

***Table 2: The MDRD equation for eGFR[1]***

$$GFR = 186 \times (S_{CR} \div 88.4)^{-1.154} \times age^{-0.203}$$

(Female: multiply result by 0.742; African-Caribbean's: multiply result by 1.212)
Note: Ethnicity factors have not yet been calculated for other ethnic groups.

eGFR is reported in mL/min/1.73 $m^2$ and so is normalised for a body surface area of 1.73 $m^2$. It explains what the person's kidneys would be capable of clearing if he or she had a body surface area of 1.73 $m^2$. This gives a convenient method of consistent reporting of eGFR which can be related to renal function and stages of CKD.

*Some areas in New Zealand are not currently reporting eGFR. An online and downloadable eGFR calculator is available from http://www.kidney.org.au/Default.aspx?tabid=95*

***Interpretation of eGFR***

Values of eGFR with the corresponding grade of kidney disease and an action plan are presented on page 19.

The indications for referral to a nephrologist are:

- eGFR < 30 mL/min/1.73 $m^2$
- Rapidly declining kidney function (> 15% decrease in eGFR over three months irrespective of baseline value)
- Proteinuria > 1 g/24 hrs
- Glomerular haematuria
- Kidney disease and hypertension that is difficult to control
- Diabetes and eGFR < 60 mL/min/1.73 $m^2$

People with marginal results (i.e. around 60 mL/min/1.73 $m^2$) should be assessed for other risk factors and signs of kidney disease, then re-checked after a few months. This is especially important in populations at high risk of renal disease in which the MDRD equation has not been validated (e.g. Māori and Pacific peoples)

***Limitations of eGFR[2]***

There are a number of clinical situations where eGFR results may be unreliable and/or misleading. These are;

- Acute changes in kidney function (e.g. acute renal failure)
- Dialysis dependent patients
- Exceptional dietary intake (e.g. vegetarian diet, creatine supplementation, high protein diet)
- Extremes of body size
- Disease of skeletal muscle. Paraplegia, amputees and those with very high muscle mass.
- Age less than 18 years.
- Presence of severe liver disease
- eGFR values above 60 mL/min/1.73 $m^2$
- eGFR has not been validated in Māori, Pacific Island and Asian people.
- The use of eGFR has not been validated for the adjustment of drug dosages. The Cockcroft-Gault equation is still recommended for this.

*Adapted from www.kidney.org.au*

***Differences between the Cockcroft-Gault equation and eGFR results***

- The Cockcroft-Gault equation requires the person's weight (preferably Lean Body Weight) for the calculation. eGFR is reported automatically without details of the person's weight.
- eGFR is normalised to a value in mL/min/1.73 $m^2$ (normal adult Body Surface Area) whereas the Cockcroft-Gault equation will give an estimate of actual GFR i.e. it is not normalised. This means there could be significant differences in the two values in people at extremes of body size.
- eGFR gives a normalised estimate of renal function whereas creatinine clearance gives an estimate of actual GFR.
- eGFR does not give an accurate estimation of renal function above values of 60 mL/min.
- eGFR has not been validated for drug dose adjustment but the Cockcroft-Gault has been used extensively for this for many years. Drug datasheets advise dose adjustments according to values of creatinine clearance.

***Other evidence of kidney damage may include:***

- Persistent microalbuminuria
- Persistent proteinuria
- Persistent haematuria (after exclusion of other causes)
- Structural abnormalities of the kidneys
- Biopsy proven chronic glomerulonephritis

***References and bibliography.***


1. Kidney Health Australia. eGFR support services http://www.kidney.org.au/HealthProfessionals/eGFRSupportResources/tabid/96/Default.aspx
2. Kidney Health Australia http://www.kidney.org.au/
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002; 39 (2 Suppl 1): S1–S266.
4. British National Formulary (BNF). BMJ Publishing Group and Royal Pharmaceutical Society of Great Britain. March 2007.
5. Devaney A, Ashley C, Thomson C. How the reclassification of kidney disease impacts on dosing adjustments. Pharm J 2006; 277: 403–4.