

WA.MSG 'Dose calculations for drugs cleared by glomerular filtration' quick reference guideline

- The clearance of many drugs and their metabolites depends on renal function; this is especially important for drugs where the gap between efficacy and toxicity is narrow.
- Doses of renally cleared drugs need careful adjustment if they are prescribed for patients with impaired renal function.
- The estimated Glomerular Filtration Rate (eGFR) provided by pathology laboratories, should NOT be used to adjust doses of medicines.
- For adult patients the Cockcroft-Gault formula (Box 1) and for paediatric patients the Bedside Schwartz Equation (Box 2), should be used to estimate renal function for purposes of calculating doses of drugs cleared by glomerular filtration.

Box 1. Adult patients: Cockcroft-Gault formula

$$\text{Creatine Clearance (CrCl)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{0.815 \times \text{serum creatinine (micromol/L)}} \quad [\times 0.85 \text{ for females}]$$

NB weight is Actual Body Weight (ABW) or Lean Body Weight (LBW) whichever is the lower.

NB In patients who are overweight using the Adjusted Body Weight (AdjBW) calculated using the patient's Lean Body Weight (LBW) and their Actual Body Weight (ABW) has been shown to be most accurate in predicting CrCl. (See Position Statement - extended guideline)

Box 2. Paediatric patients: Bedside Schwartz Equation

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 36.5 \times \text{height (cm)} / \text{serum creatinine (micromol/L)}$$

***Patients with unstable renal function and patients on renal replacement

These estimates are less reliable when renal function is unstable e.g. in ICU, acute renal impairment and febrile neutropenia and in the following patient populations:

- age greater than 70 years
- ethnicity (e.g. Asian)
- low muscle mass (e.g. elderly, amputee, malnourished patients)
- low intake of dietary protein (e.g. vegan)
- obesity

In these patients, where there is evidence of renal inefficiency, thoughtful clinical judgement should be used when deciding on appropriate drug dosing adjustments. Specialist advice should also be sought for patients on renal replacement therapy as creatinine levels are unreliable in these patients.

April 2016

WA MEDICATION SAFETY GROUP (WAMSG) ALERT

Dose calculations for drugs cleared by glomerular filtration

Position statement

The WAMSG wishes to draw attention to the laboratory advice that the Cockcroft-Gault formula (calculator available in electronic versions of the Australian Medicines Handbook and Therapeutic Guidelines) should be used to estimate renal function for dose adjustments in patients being prescribed drugs which are preferentially renally excreted.

The estimated Glomerular Filtration Rate (eGFR) provided by pathology laboratories, should **NOT** be used to adjust doses of medicines.

Background

The dose of renally excreted drugs may need to be reduced when renal function is impaired. The general principle is that the reduction in dose is proportional to the loss of renal function.

The estimated glomerular filtration rate (eGFR) provided by most pathology laboratories is calculated using the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) formula.¹ The CKD-EPI eGFR is more accurate at estimating renal function and stratifying risk of long term outcomes (e.g. mortality) than other formulae, however current guidelines,² based on historical usage data, recommend that the Cockcroft-Gault formula be used to estimate renal function for dose adjustments of drugs which are preferentially renally excreted.

The Cockcroft Gault estimate of renal function can be ordered from pathology laboratories or alternatively can be calculated by the prescriber. (Box 1.)

In patients who are overweight using the Adjusted Body Weight (AdjBW) calculated using the patient's Lean Body Weight (LBW) and their Actual Body Weight (ABW) has been shown to be most accurate in predicting CrCl.³

Limitations of the CKD-EPI and Cockcroft-Gault formulae to estimate renal function

Both the CKD-EPI and Cockcroft-Gault equations produce less reliable estimates of renal function when renal function is unstable e.g. in ICU, acute renal impairment and febrile neutropenia and in the following patient populations:

- age greater than 70 years
- ethnicity (e.g. Asian)
- low muscle mass (e.g. elderly, amputee, malnourished patients)
- low intake of dietary protein (e.g. vegan)
- obesity

In these patients, the estimation of GFR by either method could lead to overestimation of GFR. If there is evidence of renal insufficiency in the populations listed above, caution and thoughtful clinical judgement should be used when deciding on appropriate drug dosing adjustments.

Specialist advice should also be sought for patients on renal replacement therapy as creatinine levels are unreliable in these patients.

Paediatric patients

Cockcroft-Gault equation should not be used for children <18 years old.

Schwartz equation estimates renal function by calculating eGFR and can be used to guide medication dosing in children older than 1 year with renal impairment.

Creatinine-based “Bedside Schwartz” Equation (2009)⁴ (Box. 2) is an updated Schwartz equation designed for use with enzymatic creatinine assays (isotope dilution mass spectrometry (IDMS) - traceable assays) and replaces the previous formula developed using the alkaline picrate (Jaffe) method derived creatinine values.

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 36.5 \times \text{height (cm)} / \text{serum creatinine (micromol/L)}$$

It should be noted that the rate of creatinine clearance does not always accurately represent GFR; creatinine may be cleared by other renal mechanisms in addition to glomerular filtration and serum creatinine concentrations may be affected by non-renal factors (e.g. age, gender, race, body habitus, illness, diet). In addition, the equation was developed based on a limited population (CKiD cohort, n= 349) and may either over- or underestimates the renal function of a specific patient. For GFR greater than 75mL/min/1.73m², there can be lack of precision in estimating GFR using this equation. Therefore, the equation should be used in the clinical context of patient-specific factors noted and decisions regarding dose must be made on clinical judgement.

***Drugs with narrow therapeutic indices

Dose adjustments are especially important for renally excreted drugs with a narrow therapeutic index and for these drugs, drug concentrations (where possible) should be carefully monitored. This includes but is not restricted to:

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| • Antibiotics | aminoglycosides (e.g. gentamicin) |
| • Anticoagulants | low molecular weight heparins (e.g. enoxaparin) |
| • Antivirals | famciclovir, aciclovir, valaciclovir, valganciclovir, ganciclovir |
| • Hypoglycaemic drugs | glimepiride, insulin |
| • Cardiac drugs | digoxin, flecainide |
| • Cytotoxics | carboplatin, cisplatin, cyclophosphamide, methotrexate and fludarabine |
| • Psychotropics/anticonvulsants | lithium, amisulpride, gabapentin, levetiracetam |

The use of reputable web sites to aid the calculation are also recommended for example the carboplatin dose calculator that can be accessed at

<http://medicineworld.org/physicians/oncology/carboplatin-dose-calculator.html>

Health services are requested to:

- Communicate this Alert to all personnel responsible for calculation of drug dosing in patients with renal dysfunction by both paper and electronic means, and to include an explicit instruction that eGFR must not be used for this purpose.
- Prescribers should receive instruction at orientation, to be reinforced by supervising staff at regular intervals, on the use of the Cockcroft-Gault formula for dosage adjustment at the bedside and/or provided with tools to assist in this task.

The information in this note is based on current guideline groups which recommend using the Cockcroft-Gault formula for drug dosing until more clinical studies with other eGFR formula are conducted and endorsed.

References

1. The Australasian Creatinine Consensus Working Group, Chronic Kidney Disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations, Med J Aust 2012; 197(4);1-5
2. Therapeutic Goods Administration. Medicines Safety Update, Volume 3, Number 3, June 2012. Renal function in prescribing. Available at <http://www.tga.gov.au/publication-issue/medicines-safety-update-volume-3-number-3-june-2012#renal> [Accessed January 2016]
3. Winter M A, Guhr K N, Berg G M. Impact of Various Body Weights and Serum Creatinine Concentrations on the Bias and Accuracy of the Cockcroft-Gault Equation. Pharmacotherapy 2012; 32(7); 604-612.
4. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equation to estimate GFR in children with CKD, J Am Soc Nephrol. 2009;20(3):629-637

Appendix

Box 1. Adult patients: Cockcroft-Gault formula

$$\text{Creatine Clearance (CrCl) = } \frac{(140 - \text{age}) \times (\text{weight in kg})}{0.815 \times \text{serum creatinine (micromol/L)}} \quad [\text{x } 0.85 \text{ for females}]$$

NB weight is Actual Body Weight (ABW) or Lean Body Weight (LBW) whichever is the lower.

Lean Body Weight (LBW)

$$\text{Adult males: Lean Body Weight (LBW) in kilograms} = \frac{9270 \times \text{Weight (kg)}}{6680 + (216 \times \text{BMI})}$$

$$\text{Adult females: Lean Body Weight (LBW) in kilograms} = \frac{9270 \times \text{Weight (kg)}}{8780 + (244 \times \text{BMI})}$$

$$\text{Body Mass Index (BMI) (kg/m}^2\text{)} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

(An electronic LBW calculator is available in eTherapeutic Guidelines)

Adjusted Body Weight (AdjBW)

$$\text{AdjBW} = \text{LBW} + 0.4 (\text{ABW} - \text{LBW})$$

For males:

$$\text{LBW (kg)} = 50 + (0.906 \times (\text{height in cm} - 152.4))$$

For females:

$$\text{LBW (kg)} = 45 + (0.906 \times (\text{height in cm} - 152.4))$$

Box 2. Paediatric patients: Bedside Schwartz equation

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 36.5 \times \text{height (cm)} / \text{serum creatinine (micromol/L)}$$