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SPECIAL REPORT

Estimation of kidney function for medication dosing in adult patients with chronic kidney disease: a practice update

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Abstract

Chronic kidney disease (CKD) is a major health concern with a growing disease burden and inequalities in access to treatments. Glomerular filtration rate (GFR) is accepted as the best overall measure of kidney function and is considered the most important measure for medications cleared by the kidneys. In clinical practice, equations that estimate GFR using validated prediction equations are routinely used. This practice update was developed by a Working Group comprising clinical pharmacists representing the Society of Hospital Pharmacists of Australia (SHPA) Specialty Practice streams of Nephrology, Oncology and haematology, Critical care and Infectious diseases. It is intended to provide practical recommendations for clinical pharmacists who use equations to estimate GFR for medication dosing decisions. The limitations of the various equations in use — such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the Cockcroft–Gault equation and Modification of Diet in Renal Disease — are summarised and compared to direct measures of kidney function using exogenous markers. The CKD-EPI equation is recommended to be used routinely as a primary measure of kidney function. Dose adjustments should also consider medication-specific, patient-related, and disease-related characteristics. Kidney function and the response to therapy should be continuously assessed by monitoring the signs, symptoms and disease outcomes, the emergence of adverse reactions or medication-induced disorders and use therapeutic drug monitoring (if available) to adjust doses accordingly.

Keywords: chronic kidney disease, medication dosing, eGFR, estimation of kidney function, glomerular filtration rate.

INTRODUCTION

Chronic kidney disease (CKD) is a major health concern with a growing disease burden and inequalities in access to treatments.[1] In Australia, approximately 1.7 million adults (1 in 10) have CKD.[2] For those living in rural and remote areas, rates are much higher and the

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prevalence of CKD among Aboriginal and Torres Strait Islander Peoples is twice that of non-Indigenous adults due to social determinants of health.[3] Despite this, fewer than 10% of people are aware they have CKD,[4] leading to delayed initiation of therapies able to slow the progression of CKD. At risk people also have an increased likelihood of inappropriate medication dosing, which may predispose to further acute kidney injury (AKI).[5] Medication-induced AKI accounts for up to 20% of AKI cases and can contribute to the development of incident CKD or progression of existing CKD.[5] Hence, accurate estimation of kidney function to detect AKI or CKD is necessary for optimal treatment selection, dose adjustments and the prevention of adverse medication-related outcomes, including loss of kidney function and other metabolic complications.[6]

Glomerular filtration rate (GFR) is accepted as the best overall marker of kidney function and is considered the most important descriptor of clearance for renally cleared medicines. Validated prediction equations that estimate GFR (eGFR) are routinely used in clinical practice.

The Society of Hospital Pharmacists of Australia (SHPA) has produced standards of practice in nephrology,[6] oncology and haematology,[7] critical care[8] and infectious diseases[9] to describe pharmacy practice standards for the provision of safe and optimal use of medicines in patients. This practice update was developed by an SHPA Working Group comprising clinical pharmacists representing these Specialty Practice streams. It is intended to provide practical recommendations for clinical pharmacists who use equations to estimate GFR for medication dosing decisions. It highlights the many limitations of these equations and discusses situations that may lead to bias or imprecision.

GLOMERULAR FILTRATION RATE

GFR is the rate at which the kidney glomerulus filters plasma to produce an ultrafiltrate and can be assessed by measuring clearance of exogenous filtration markers or serum concentrations of endogenous filtration markers.[10]

Measurement of GFR Using Exogenous Filtration Markers

The gold standard for precise kidney function assessment is the measurement of GFR using an exogenous marker and serial measurements. The process is time-consuming, costly and largely unavailable or not required for the purpose of medication dosing decisions in everyday clinical practice. Exogenous filtration markers used for this purpose are freely filtered by the glomerulus, neither reabsorbed or secreted by the tubules and examples include inulin, sinistrin, iohexol and iothalamate.[10]

Estimating GFR Using Serum Concentrations of Endogenous Filtration Markers

To support dosing decisions of renally cleared medications, GFR values are estimated (eGFR) using equations that use serum concentrations of endogenous filtrations makers. The two most commonly used endogenous filtration markers are creatinine and cystatin C.

Creatinine

Creatinine is a waste product formed by muscle metabolism that is cleared from the blood primarily by glomerular filtration, with tubular secretion accounting for less than 15% of clearance, making it a reasonable filtration marker in most scenarios.[10]

While changes in serum creatinine concentration can reflect a change in glomerular function, there are times when this change is not an accurate representation. The following situations will lead to imprecision in the eGFR when any creatinine-based estimating equation is used.

Factors Affecting Creatinine Generation: Fenofibrate and diets very high in protein or those which include creatine or protein supplements above the recommended daily intake, can increase the metabolic production of creatinine.[10] Intense exercise that leads to muscle metabolism can also lead to a rise in serum creatinine concentrations. These scenarios can elevate serum creatinine concentrations and lead to a false perception of a reduced GFR. Conversely, clinical scenarios exist where a reduction in a patient's muscle mass, such as prolonged periods of immobility, paralysis or connective tissue disorders, may produce a low serum creatinine concentration. These instances may lead to a false sense of adequate kidney function due to a low serum creatinine concentration.

Factors Affecting Tubular Secretion of Creatinine: Medicines including cimetidine, trimethoprim, dolutegravir and tyrosine kinase inhibitors are well recognised to cause an increase in serum creatinine concentration by inhibition of cellular transporter proteins in the proximal tubule.[10–13] The resulting increased serum creatinine concentration leads to an artificially reduced eGFR or

pseudo-AKI that does not reflect a true reduction in GFR and will correct when the medicine concerned is stopped.

Cystatin C

Cystatin C is a low molecular weight protein that is produced by the body at a constant rate. It is freely filtered by the glomerulus then metabolised after tubular reabsorption, resulting in only small amounts being excreted in the urine.[14] For this reason, urinary cystatin C concentrations cannot be measured to estimate GFR; however, equations that incorporate serum cystatin C concentrations have been developed. Cystatin C is less affected by muscle mass and diet than creatinine, but carries its own set of unique limitations that need to be considered. Equations that incorporate both creatinine and cystatin C values have been shown to outperform those that include only one or the other.[10]

Whilst widespread use of estimating equations that include cystatin C is currently limited by cost and availability, they have been used selectively in patients with muscle wasting or chronic illness where an accurate estimate of their kidney function is considered important for clinical decision making.

Equations to Estimate Kidney Function

All methods for estimating kidney function are associated with systematic or random errors due to the clearance mechanism itself, exogenous filtration marker used and the assays themselves.[10] There is no compelling evidence of the superiority of any given method to guide medication dosing for all patient groups.[15] Clinicians should have access to at least one GFR estimate and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is currently considered the most accurate method for estimation of GFR.[15]

A brief history of the most commonly used equations is given below. All equations discussed use serum creatinine concentration as a filtration marker and are limited by conditions that affect creatinine generation and tubular secretion, as outlined above.

Importantly, some equations such as the CKD-EPI and the Modification of Diet in Renal Disease (MDRD) are indexed for a standardised body surface area (BSA) of 1.73 m^2. When used for medication dosing in obese or underweight patients, the indexed eGFR should be adjusted for the patient's actual BSA to avoid incorrect dosing, as their BSA differs from a standardised BSA.[16]

Cockcroft–Gault Equation

The Cockcroft–Gault (CG) equation estimates creatinine clearance (CrCl) as a surrogate marker of a patient's kidney function and was published in 1976.[16] This equation was ground-breaking for its ability to estimate a patient's CrCl using a single serum creatinine concentration and without having to collect urine, as is required for measured CrCl (mCrCl). The benefits were considered highest for supporting dosing of potentially nephrotoxic medicines.[17] The population used to derive this equation comprised 249 Caucasian adult men, aged between 18–92 years, who were medical inpatients in a veterans' hospital in Canada.[17] The CG equation uses easily accessible patient characteristics in conjunction with a serum creatinine concentration to generate an estimated CrCl (eCrCl). There are inherent limitations to this equation resulting in variations driven by patient characteristics such as age, sex, weight, muscle mass, disease state, diet and certain therapies.[2,18–22] It is important to note that no women were included in the original equation derivation study. To compensate for women having different relative amounts of fat and muscle compared to men, a 15% reduction of predicted CrCl was arbitrarily included based on previous study estimations.[18]

The CG equation is remarkable for its longevity and its place in the regulatory and academic frameworks of pharmacy and medicine over the last 40 years.[17] Even so, clinical practice globally is moving away from using the CG equation routinely.

The Modification of Diet in Renal Disease Equation

The MDRD equation, published in 1999, estimates GFR. It was developed from 1600 patients with the view of simplifying the estimation of kidney function to allow automatic reporting based on readily collected laboratory results to improve identification of kidney disease in individuals.[23] The MDRD equation includes the independent variables age, sex, Black and non-Black race, and serum creatinine.[23] Limitations of the MDRD equation are that it underestimates kidney function at greater than 60 mL/min/1.73 m^2 and greater than 10% of all estimated results varied by more than 30% to a measured GFR, hence newer equations were considered more appropriate.[24]

The Chronic Kidney Disease Epidemiology Collaboration Equation

The original 2009 CKD-EPI equation estimates GFR and was developed using a large database pooled from 10 studies and validated using the data pooled from 16 additional studies.[25]

The original CKD-EPI equation included age, race and sex as surrogates for non-GFR determinants of serum creatinine.[24] These variables are associated with muscle mass, the main determinant of creatinine

generation. Imprecision of GFR estimates suggests that age, race and sex do not account for all variation in non-GFR determinants of serum creatinine and may be secondary to non-GFR determinants of creatinine.[24,26–28] The CKD-EPI equation provided on Australian pathology reports does not include an adjustment for race and similarly, internationally, there is a movement to adopt a newer version of the 2021 CKD-EPI that no longer has a race adjustment.[29]

The CKD-EPI equation is considered more accurate than the MDRD study equation and it has a lower bias for GFR greater than 60 mL/min/1.73 m^2,[22] making it more reliable for CKD staging in primary care. For this reason, CKD-EPI has been the predominant equation used to report eGFR in Australian clinical laboratories over the past decade. It accounts for standardisation of the creatinine assay that was introduced in 2010.[28,30]

There is ongoing opportunity for refinement of this equation to incorporate disease- and medication-level parameters that may improve its applicability to specific patient groups.[18,24,31,32] In such populations developing improved eGFR equations that incorporate other parameters (e.g. blood glucose concentrations in patients with diabetes) would be desirable.[18,32]

CLINICAL DECISION MAKING FOR MEDICATION DOSING IN PATIENTS WITH CKD

Some medicines are contraindicated below certain thresholds of GFR and many medicines that are cleared by the kidneys require dose adjustments.[29] Medication dosing decision in patients with CKD is performed on a case-by-case basis. Factors such as baseline kidney function, duration and magnitude of the change to kidney function should be considered. The burden of adverse medication reactions is high in patients with CKD, particularly those with eGFR < 30 mL/min/1.73 m^2.[33]

Calculating an eGFR or eCrCl to guide initial dosing is only one part of this decision-making process.[28] The CG equation and eCrCl have been used for dosing adjustments in many clinical trials and subsequently included in the product information (PI) for the relevant medicines when licensed. In practice, using eGFR (CKD-EPI) in place of eCrCl (CG) is likely to only result in small changes in estimates of kidney function and negligible clinical significance when making dosing decisions that should utilise a broader thought process.

It is also important to recognise that dosing recommendations found in the PI, whilst helpful, often fail to include updated information that may support dosing at reduced levels of kidney function that has come about from additional clinical trials post-marketing. Medication dosing resources, along with information found in the primary literature, may be more useful to guide practice, particularly in patients with advanced CKD, who are often excluded from original research.

For patients with kidney dysfunction, dosing at the specific thresholds for dose change recommendations can be complex and have significant impact on these patients. For example, a threshold of 30 mL/min is used for many medicines, with eGFR/eCrCl values below this requiring a dose decrease. However, the inaccuracy of all equations means that dose reduction should consider additional medication-specific, patient-related and disease-related characteristics (Tables 1–3). The potential impact of toxicity from the medicine being dosed needs to be weighed against the risk of underdosing, especially in critical situations such as antimicrobial therapy in sepsis.

Following the initial medication dosing decision, the response to therapy should be continuously assessed by monitoring the signs, symptoms and disease outcomes. For medications with a narrow therapeutic index, where a small change in medication concentration can cause toxicity or loss of efficacy, validated biomarkers or therapeutic drug monitoring should be used in addition to close monitoring for clinical response. Ongoing assessment of kidney function is, of course, essential.

Pharmacokinetic and Pharmacodynamic Considerations in Patients with CKD

The pharmacokinetics of many medications can be altered in patients with CKD, although for some no dose changes are required.

A decrease in glomerular filtration or tubular secretion will reduce clearance of medications as well as the active and toxic metabolites typically cleared by those mechanisms.[15] Some have significant tubular secretion, which may result in higher clearances than their eGFR may otherwise suggest, such as amoxycillin, cefalexin, meropenem and metformin.[34–36] Furthermore, the activity of kidney drug transporters may be affected by pharmacogenetic differences and drug–drug interactions.[37] For example, inhibition of apical efflux transporters may reduce drug exit from renal tubular cells, leading to accumulation, nephrotoxicity and systemic toxicity.[38] Additionally, some medications have increased clearance via other elimination routes, for example increased transintestinal clearance of ciprofloxacin has been described in severe kidney dysfunction providing an 'extrarenal safety factor', meaning that linear dose adjustments with decreasing GFR would be highly inappropriate.[39]

Table 1 Medication-specific characteristics

What to ask	What to consider and/or action
What is the proportion of the medication eliminated by the kidney?	The medication is deemed to be eliminated via the kidneys when >30% of the medication or its active metabolite, is eliminated by the kidneys In patients with impaired kidney function use alternative medication or reduce the dose and/or extend dosing interval. Follow the dosing guidelines, monitor kidney function and patient response for effectiveness and safety, and adjust accordingly
Is the medication nephrotoxic (directly damaging to the kidney)?	Avoid nephrotoxic medications in elderly patients, patients with AKI and/or CKD, kidney transplant recipients, and patients on peritoneal dialysis with residual kidney function In patients on haemodialysis, nephrotoxicity is not relevant (e.g. NSAID)
Is the patient taking any other potentially nephrotoxic medication(s)?	Combinations of nephrotoxic medications increase risk for kidney injury (e.g. NSAID and radiocontrast, aminoglycoside and cisplatin, NSAID, ACEI/ARB and diuretic)
What are the pharmacokinetic differences in patients with normal kidney function compared to impaired kidney function?	Account for altered pharmacokinetics noting that CKD causes downregulation of hepatic cytochrome P450 metabolism and drug transporters Decreased protein binding due to hypoalbuminemia leads to increased free fraction of the medication (pharmacologically active)
Does the medication have active or toxic metabolites that are predominantly eliminated by the kidneys?	Medications that are predominantly metabolised by the liver to pharmacologically active or toxic metabolites that are excreted by the kidneys can accumulate in patients with kidney impairment Example of active metabolites: Morphine → morphine-6-glucuronide → CNS side effects Example of toxic metabolites: Pethidine → norpethidine → CNS effects (seizures)
Are there dosing guidelines for impaired kidney function available for the medication in question?	Adjust the doses of the medication(s) that are eliminated by the kidneys according to the guidelines
Does the medication have a narrow therapeutic index?	A small change in plasma concentrations can lead to toxicity or a less efficacious treatment Available estimates of kidney function alone will be inadequate to guide dosing and the use of validated biomarkers or therapeutic drug monitoring should be used, in addition to close monitoring for clinical response
Is there validated therapeutic drug monitoring available?	Monitor serum concentrations and adjust doses according to validated target ranges
What are the risks of adverse effects from accumulation?	Be familiar with the incidence of adverse effects in patients with CKD and monitor accordingly
Has the patient been taking any medications that inhibit tubular drug transporters?	Extensive uptake of potentially nephrotoxic medications by tubular cells *via* both apical and basolateral transport systems can lead to kidney injury Inhibition of apical efflux transporters such as multidrug-resistance protein transporters, human multidrug and toxin extrusion protein transporters (hMATE1, hMATE2) and P-glycoprotein diminishes drug exit from renal tubular cells leading to accumulation, nephrotoxicity and systemic toxicity
Has the patient been taking any medications known to interfere with renal creatinine handling?	Some medications may reduce tubular secretion of creatinine (and corresponding increase in serum creatinine) that results in a false reduction in reported eGFR. Some examples include trimethoprim, cimetidine and tyrosine kinase inhibitors

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; CNS = central nervous system; eGFR = estimated glomerular filtration rate; hMATE1 = human multidrug and toxin compound extrusion-1; hMATE2 = human multidrug and toxin compound extrusion-2; NSAID = non-steroidal anti-inflammatory drugs.

Table 2 Patient-related characteristics

What to ask	What to consider and/or action
Is the patient elderly, paediatric, with extremes of muscle mass, pregnant, or a transgender person?	GFR drops by an estimated 1 mL/min per year after 40 years of age Extremes of muscle mass to be considered include amputation, muscle wasting or bodybuilding Pregnant patients and patients with amputations require special consideration Transgender persons on hormonal therapy require estimation of GFR using male and female sexes and these GFR values are used as a range
What is the patient's baseline eGFR and severity of kidney impairment?	Determine the Kidney Disease Improving Global Outcomes (KDIGO) classification of kidney impairment: Stages 1–5, based on eGFR and presence of kidney damage[73] If the patient has any clinical condition in which non-GFR determinants may lead to the imprecision of eGFR: • Use the best method to estimate GFR, such as the de-indexed CKD-EPI in patients who are overweight or obese • Redetermine the patient's CKD stage based on de-indexed GFR for appropriate dosing of medications predominantly eliminated by the kidneys
Is kidney impairment acute, chronic, or acute-on-chronic?	All estimating equations that incorporate serum creatinine are inaccurate in AKI and acute-on-chronic kidney impairment (non-steady state)
Is eGFR stable, rising or declining?	eGFR is stable in CKD so adjust the doses of medications that are eliminated by the kidneys according to the eGFR and monitor kidney function and side effects Be aware of the inaccuracy of a single point estimate when kidney function is rapidly changing as creatinine is not at steady state If the eGFR is falling, the decline in eGFR is less than the decline in mGFR. In AKI, the risk of overdosing is high, therefore some medications need to be withheld or their doses reduced (dose as per GFR < 10 mL/min) Conversely, if the eGFR is rising, the rise in eGFR is greater than the rise in mGFR. After recovery of GFR (e.g. after AKI or in the post-transplantation phase) there is a risk of underdosing of medications cleared by the kidneys The more rapid the change in eGFR, the larger the change in GFR When the eGFR reaches a new steady state, it more accurately reflects measured GFR If kidney function is rapidly changing, consider measuring GFR. Monitor U&E and re-assess kidney function daily. Monitor blood levels of the relevant medications
Is the patient obese (BMI > 30 kg/m^2) or underweight (BMI < 18.5 kg/m^2)?[a]	Use CKD-EPI eGFR adjusted as follows: • BMI 18.5–30 kg/m^2 → use eGFR [mL/min/1.73 m^2] • Obese BMI > 30 kg/m^2 or weight > 120 kg → use de-indexed eGFR (absolute eGFR) [mL/min] • Underweight BMI < 18.5 kg/m^2 or weight < 60 kg → use de-indexed eGFR (absolute eGFR) [mL/min][b]
Is the patient dehydrated?	SCr may be increased in patients who are dehydrated due to haemoconcentration To prevent AKI, some medicines may need to be temporarily withdrawn (SAD MANS [**S**ulfonylurea, **A**CEI, **D**iuretics, **M**etformin, **A**RB, **N**SAID, **S**GLT2I])
Is the patient septic?	Approximately 60% of patients with sepsis or septic shock develop AKI and this is associated with poor clinical outcomes Monitor kidney function and closely consider what therapies need to be discontinued or withheld
Does the patient have liver impairment?	Liver dysfunction can affect medication metabolism, clearance and elimination Hypoalbuminemia may alter protein binding, resulting in greater medication exposure and toxicity due to increased free fraction of medication (not bound to albumin) Prodrugs that require conversion to the active metabolites in the liver may lose therapeutic efficacy due to reduced enzyme activity in liver impairment Consider using cystatin C to estimate eGFR by using alternative CKD-EPI

Table 2 (*continued*)

What to ask	What to consider and/or action
Is the patient a kidney transplant recipient?	Most patients will only receive a single kidney transplant, making them more susceptible to future acute kidney insults. Choose medications carefully and consult transplant team if unsure of safety
What modality of dialysis is a patient receiving?	Estimating equations will be inaccurate in this population and should not be used to guide medication dosing decisions Adjust the doses according to information available for the individual's dialysis modality and frequency of dialysis
Do any pharmacogenomic factors need to be considered?	Cytochrome P450 polymorphism may affect medication metabolism. Medications that exhibit polymorphic metabolism may be at much higher risk of adverse medication reactions in people with CKD

ACEI = angiotensin converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin receptor blocker; BMI = body mass index; CG = Cockcroft–Gault; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; mGFR = measured glomerular filtration rate; NSAID = non-steroidal anti-inflammatory drugs; SCr = serum creatinine; SGLT2 = sodium glucose cotransporter 2 inhibitor; U&E = urea and electrolytes.
[a]Body mass index (BMI) = weight (kg)/height $(m)^2$.
[b]Absolute GFR = (body surface area [BSA] indexed eGFR × patient's BSA)/1.73 m^2 = mL/min.

Table 3 Disease-related characteristics

What to ask	What to consider and/or action
What is the indication?	Use medications only if there is a definite indication
	Choose the medication with minimum nephrotoxicity
Is the patient critically ill?	Consider the hospital setting such as regular ward, high dependency or ICU
Is there clinical significance to any underdosing?	Consider the acuity and the severity of the disease that requires treatment
	Unnecessary decreases in dosage may result in undertreatment
Is a single dose or more than one dose required?	Administration of inappropriately high doses of medications in patients with impaired kidney function can result in toxicity after multiple dosing, rather than after the first dose
What is the duration of therapy?	The risk of adverse medication effects increases with the duration of therapy
Are other treatment options more suitable for someone with kidney impairment?	If possible, use medications that are not or minimally eliminated by the kidneys

ICU = intensive care unit; U&E = urea and electrolytes.

Some hepatically cleared medications may also have altered clearances in patients with CKD that are unrelated to kidney function itself. For example, cytochrome P450 3A4 (CYP3A4) isoenzyme activity is reported to decrease in activity during end-stage kidney disease (ESKD), possibly as a result of uraemia,[40] but a 27% increase in activity of CYP3A4 may occur post-haemodialysis in ESKD patients.[35] To this end, consideration of other disease processes is required given that many CKD patients have additional comorbidities that can affect medication dosing requirements. Decreases in clearance will result in a prolonged medication half-life.

Changes in medication clearance relating to kidney function do not influence loading doses where these are recommended, but can influence ongoing maintenance doses of the same medications (vancomycin, teicoplanin, voriconazole, digoxin).[41]

Volumes of distribution (Vd) may also be increased by CKD itself, although most commonly they are unchanged. Any Vd change is typically not of a sufficient magnitude to require dose adjustment,[36] although caution regarding other comorbidities patients may have and their association with altered volumes of distribution and altered dosing requirements should be considered where relevant, e.g. obesity.

Another key consideration of dosing in patients with CKD is the pharmacodynamics of the medication by understanding the medication-specific goals of therapy.[15] Depending on the relationship between medication concentration and clinical response, the goals of therapy may include the maintenance of a peak, trough or average steady-state concentration or the maintenance of the time above the minimum inhibitory concentration (MIC) or the ratio of the drug area under the concentration time curve (AUC) to the MIC.[15] Whilst most medications require a minimum threshold exposure throughout the dosing interval for continuous clinical effects, particularly for chronic comorbidities, this is not always the case. Using antimicrobials as exemplars, some antibiotics have concentration-dependent bacterial killing (e.g. aminoglycosides) whereas others have time-dependent bacterial killing (e.g. beta-lactams). For concentration-dependent medications, a peak concentration to MIC ratio (peak/MIC) >10 is associated with maximal bacterial killing and a higher likelihood of clinical cure. However, for beta-lactams, maintaining concentrations above the MIC throughout the dosing interval is more relevant, with high peak concentrations conferring no clinical benefit or additional bacterial killing. Concentrations associated with medication toxicity (toxicokinetics) may not follow the same pattern as clinical efficacy/bacterial killing and may be more associated with either peak or trough concentration, or potentially total medication exposure. It follows for the clinician that choices for the adjusted dose in CKD patients should account for the pharmacodynamic (and toxicokinetic) characteristics of a medication to ensure the highest likelihood of clinical efficacy and lowest likelihood of toxicity. Optimising dosing strategies of antimicrobials based on pharmacokinetic/pharmacodynamic principles and specific medication properties has been recommended for critically ill patients with sepsis and obesity.[33,42]

The medication-related characteristics to be considered for estimation of kidney function and dosing considerations are summarised in Table 1.

Dosing Considerations for Specific Medications

Dosing of Antibiotics Requiring Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is the process of measuring medication concentrations in a biological matrix typically blood, with subsequent dosing adjusted to ensure that the patient achieves an exposure (measured concentration/s) that is associated with efficacy and a low likelihood of toxicity. Various medications are recommended to have dosing supported by TDM, with medications of narrow therapeutic index like glycopeptides and aminoglycosides commonly dosed in this way.[42] In these scenarios, eGFR becomes relevant for only empiric dosing (before TDM is available) and the eGFR equation that has greatest accuracy for that medication-patient combination should be used for those initial dose calculations. Thereafter, TDM should be used in preference to eGFR, as long as it is performed regularly enough, because TDM informs the precise medication exposure that eGFR seeks to predict and as such, will always be more reliable. However, TDM is not always possible, due to assay unavailability or blood sampling difficulties, and in those scenarios dosing decisions should be supplemented with eGFR.

Dosing of Direct Oral Anticoagulants

Evidence to definitively direct the preferred equation for estimating kidney function to assist with dosing of direct oral anticoagulants (DOACs) is still lacking. Although using eGFR CKD-EPI at the bedside is practical, as it is readily available, studies have shown that different equations will result in different dosing recommendations.[43–45]

A large study of 39 239 patients with atrial fibrillation (AF) investigated 11 185 patients on DOACs and 2323 on warfarin. The results showed that use of MDRD or CKD-EPI rather than CG, would result in inappropriate dosing of DOACs (mainly overdosing). The authors concluded that the CG equation should be used as the gold standard to calculate eGFR and guide dosing of DOACs.[43] These results were similar to a recent study by Rohla et al., also in 1288 AF patients.[44] Using MDRD or CKD-EPI, instead of CG, resulted in different dose recommendations for dabigatran, edoxaban, and rivaroxaban in up to 25% of the patient cohort. In patients where no concordance existed between CG and CKD-EPI, there was a different risk profile evident, with higher rates of both bleeding and thromboembolic events.[44] In contrast, a study in 6392 patients with AF concluded that although there were differences in estimating kidney function between the CG and non-CG equations, the risks of thromboembolism and major bleeding were similar to those with warfarin, regardless of which equation was used.[45]

Estimated GFR CKD-EPI can be used at the bedside for initial dosing of a DOAC. Close monitoring for efficacy and side effects is recommended. For complex patients, particularly those on longer term therapy, DOAC that has proven safety at lower eGFR should be considered, with regular review of kidney function to monitor for deterioration and appropriateness of dosing.

Dosing of Anticancer Medications

Direct measured GFR (mGFR) testing is the gold standard and is recommended to be used in a select group of anticancer medications, including carboplatin, cisplatin and methotrexate (≥500 mg/m^2), as well as in patients with extremes of body size or muscle mass, amputees or persons with paraplegia or conditions of skeletal muscle.[46] However, access to mGFR in cancer care is currently limited due to capacity in larger centres and the unavailability of mGFR at smaller services, so it is often reserved for situations that necessitate a more accurate dose (e.g. carboplatin dosing).[45] Studies in cancer settings have shown eCrCl to be less reliable than the other equations when used by the bedside for dosage selection for kidney-excreted anticancer medications when compared with the use of mGFR.[26,47]

In line with the newly developed *International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)* by eviQ and Cancer Institute NSW, it is recommended to use eGFR CKD-EPI as the standard and routine estimate of kidney function, and to use BSA-adjusted eGFR CKD-EPI for carboplatin dosing using the Calvert equation.[46] The ADDIKD was developed after an extensive and in-depth review of published literature. For individual guidance on specific medications and special populations (e.g. obesity, AKI) practitioners should refer directly to the ADDIKD and related protocols.[46]

Dosing Considerations for Specific Patient Groups

The patient- and disease-related characteristics to be considered for estimation of kidney function for medication dosing are summarised in Tables 2 and 3, respectively. A summary of recommendations for specific patient groups is given below.

Medication Dosing in an Obese Patient

Obesity is associated with increased kidney blood flow, glomerular hyperfiltration and kidney hypertrophy.[48–50] Studies have shown that the CG-based equations, even with adjustments for body weight, perform poorly in this population. When adjustment of dosage needs to be carried out at GFR levels between 30–45 mL/min, the MDRD de-indexed by BSA (also referred to as BSA-adjusted) and CKD-EPI de-indexed equations are reasonably equivalent, with good performance.[15,16,51,52]

Estimating GFR using the MDRD and CKD-EPI de-indexed by the BSA has high accuracy for obese individuals with a GFR of 30–80 mL/min.[48,51,53] eGFR CKD-EPI is indexed for standardised BSA 1.73 m^2. If using eGFR for medication dosing, the indexed eGFR should be adjusted for the patient's actual BSA to avoid incorrect dosing in obese or underweight patients.[16] The utility and accuracy of all equations decrease in individuals who are severely obese and also have GFR < 30 mL/min.[52] In these cases, mGFR is recommended, in particular when dosing medications with a narrow therapeutic index.[48,52]

Medication Dosing in Patients with Amputations

Patients with amputations have reduced body mass due to loss of muscle mass, resulting in lower values of serum creatinine, elevated CrCl and overestimated GFR that could adversely affect dosing of medications.[54,55]

Cystatin C is a preferable endogenous biomarker for estimation of kidney function in patients with amputations because it is less affected by changes in muscle mass.[10,56,57] Gold standard exogenous markers should be made more accessible in clinical practice for critical decisions surrounding dosing of high-risk medications cleared by the kidneys.[58,59]

Elbarbry et al.[54] suggest $CG_{,}$ as the only equation that incorporates weight, may provide more accurate estimation of kidney function in patients with amputations. However, weight measurements are often impractical for patients with amputations due to immobilisation, and inaccurate due to unstable fluid and food intake, oedema, and blood loss.[56] Weight measurements are also required to convert eGFR based on CKD-EPI from normalised units (mL/min/1.73 m^2) to absolute values. For medications with a narrow therapeutic index, the amputation ideal body weight should be calculated using the estimated body weight lost. It is suggested to use Osterkamp proportion numbers, where each body segment is assigned a percentage of body weight.[59,60] Future equations should rely less on weight measurements and utilise biomarkers that are less dependent on weight.[56] However, these methods have not yet been validated in patients with amputations, therefore TDM is recommended to supplement dosing calculations.[60] Caution should be exercised when using eCrCl with an estimated body weight as the estimation may not correlate with the patient's true kidney function.

If medications require dosing on BSA, such as chemotherapy, currently there is no evidence-based recommendation for calculating BSA in patients with amputations.[54] For anticancer medications, the consensus recommendation by the ADDIKD is to use mGFR.[46]

Medication Dosing in Pregnancy

Pregnancy is associated with a significant increase in GFR and may exceed the pre-pregnancy value by 50% at the end of the first trimester.[48] Of the different studies undertaken in pregnant women, including with comorbidities

such as pre-eclampsia, diabetes, and obesity, the overall comparison of equations used indicates that the CG equation using total body weight overestimates eCrCl, whilst eGFR is underestimated using either the MDRD or CKD-EPI equation.[48,61–63]

This underestimate of eGFR by both the MDRD and CKD-EPI equations was up to 20%. The underestimate was demonstrated using inulin for gold standard GFR determination.[47] The ongoing changes in kidney function duration gestation and post-partum also make it difficult to predict steady state, limiting the usefulness of eGFR further.[64]

Serial serum creatinine concentrations are recommended for monitoring kidney function in pregnancy, especially in acute illness.[63] To monitor overall trends in an individual, the eGFR can be used and should be calculated using the eGFR CKD-EPI equation.[64,65]

Medication Dosing in Transgender Persons with Kidney Disease

All equations for kidney function estimates use sex as a variable. The effects of hormone therapy on body composition and lean body mass are not well quantified and therefore the associated effects on eCrCl and eGFR are unclear.[62] For transgender persons receiving hormonal therapy it is recommended to estimate GFR using male and female sexes and then use these values as a range. Singularly applying the birth sex is not recommended.[66] As in other clinical scenarios if a truly accurate estimate of GFR is required, consideration could be given to mGFR.[66]

Medication Dosing in Critically Ill Patients

The commonly used creatinine-based kidney function calculations have demonstrated poor accuracy and precision in critically ill patients, as none were developed in this special patient population.

In a cohort of critically ill patients without AKI the utilisation of the MDRD equation and calculated CrCl (CG) were compared to a mCrCl. This comparison found a lack of accuracy and low precision when using the MDRD equation, but was limited by wide variability in patient kidney function.[67] Further analysis comparing 2 h and 24 h mCrCl with both creatinine- and cystatin C-based measurements found the creatinine-based estimations were less accurate and precise than the measured methods and the cystatin C-based equations.[68] The CKD-EPI was most accurate and precise of the creatinine calculations.

Serious uncertainty persists about the capacity of CKD-EPI to reliably identify augmented kidney clearance (CrCl > 130 mL/min/1.73 m^2), a common phenomenon in critically ill patients which has been associated with worse patient outcomes and subtherapeutic medication concentrations.[69,70]

The general disparity and lack of a 'perfect' creatinine-based calculation for critically ill patients is likely explained by the reduced production of creatinine, muscle loss secondary to immobility and, in some cases, accelerated muscle catabolism.[71,72] In these patients the importance of TDM and individualised dosing strategies based on the known pharmacokinetic/ pharmacodynamic principles of the specific medication should be utilised. When more precise measures such as mCrCl cannot be employed, the calculation of CrCl using CKD-EPI can be considered as part of a multimodal assessment of kidney function and medication dosing assessment.

CONCLUSION

Estimation of kidney function is important clinically for measuring the progression of kidney disease and for determining appropriate doses for medications cleared by the kidneys. The CKD-EPI equation is recommended to be used routinely as a primary measure of kidney function in most patient populations. Clinical judgement should be used to evaluate every situation individually based on medication-specific, patient-related and disease-related characteristics. Kidney function and the response to therapy should be continuously assessed by monitoring the signs, symptoms and disease outcomes, the emergence of adverse reactions or medication-induced disorders and TDM (if available) used to adjust doses accordingly.

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CONFLICTS OF INTEREST STATEMENT

Jason Roberts is an Associate Editor of the *Journal of Pharmacy Practice and Research* and an author of this special report. He was excluded from editorial decision-making related to the acceptance and publication of this

special report. The authors declare they have no additional conflicts of interest.

AUTHORSHIP STATEMENT

Conceptualisation: SM, CS, JL, JC, JR. Formal analysis: SM, CS, JL, JC, SO, SP, JR. Investigation: SM, CS, JL, JC, SO, SP, JR. Methodology: SM, CS, JL, JC, SO, SP, SHN, JR. Project administration: CS, JC, SHN. Resources: SM, CS, JL, JC, SO, SP, SHN, JR. Supervision: JC, SHN, JR. Validation: SM, CS, JL, JC. Writing – original draft: SM, CS, JL, JC, SO, SP, SHN, JR. Writing – review and editing: SM, CS, JL, JC, SO, SP, SHN, JR.

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Ethics approval was not required for this special report.

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OPEN ACCESS STATEMENT

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this special report as no new data were created ot anaylsed in this study.

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This activity has been accredited for 1 hour of Group 1 CPD activity (or 1 CPD credit) suitable for inclusion in an individual pharmacist's CPD plan, which can be converted to 1 hour of Group 2 CPD (or 2 CPD credits) upon successful completion of the relevant assessment activity. No: S2024/06.