

# Chronic kidney disease

## — new approaches to classification

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Recent changes to the classification of chronic kidney disease have introduced new ways of measuring renal function. This article describes differences in the techniques used and highlights the problems this may cause in practice



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**O**ver the past few years the terminology used to describe kidney disease has changed. Previously, as the kidneys became less and less able to do their normal work of cleaning the blood and producing urine from the waste products, patients were said to have chronic renal or kidney failure. The term “end stage renal failure” was used to describe those patients requiring dialysis or a transplant in order to stay alive. Chronic renal failure was categorised into mild, moderate or severe renal impairment.

However, following the UK adoption of the US Kidney Disease Quality Outcomes Initiative (K/DOQI) in 2003, these terms have been replaced by the term “chronic kidney disease” (CKD) with the patient’s level of renal impairment graded from stage 1 (near normal) to stage 5 (established renal failure or on dialysis).

End stage renal failure is now referred to as established renal failure (ERF). ERF is relatively rare, but treatment with dialysis or transplantation is expensive, costing over 2 per cent of the total NHS budget. In the UK, 110 patients per million population

start dialysis each year.<sup>1</sup> Early CKD is more common. CKD has a number of possible causes, but the effects are invariably the same, and referral of all patients with early CKD would overwhelm existing specialist renal services.

The aim of this article is to alert pharmacists and prescribers to the new classification of CKD and the subsequent clinical biochemistry laboratory reporting of estimated glomerular filtration rate (eGFR) and serum creatinine concentrations. It will explain the differences between the different measurements of renal function and highlight the problems in practice associated with these changes.

One of the biggest challenges facing all prescribers and pharmacists is adaptation and use of the new classification system to ensure safe clinical practice, especially with regard to accurate drug dosing for each patient’s degree of CKD. The grouping of CKD into five stages now supersedes and conflicts with other advice on grading of renal impairment. For example, the British National Formulary (no.52) states that “for prescribing purposes, in the BNF, renal impairment is arbitrarily divided into 3 grades”, (see

Panel 1). In our opinion, this advice is no longer reflective of clinical practice. The BNF says “Renal function is measured either in terms of glomerular filtration rate estimated from a formula derived from Modification of Diet in Renal Disease study (‘MDRD formula’ that uses serum creatinine, age, sex and race) or it can be expressed as creatinine clearance (best derived from a 24-hour urine collection but often calculated from a formula or a nomogram that uses serum creatinine, weight, sex and age). The serum creatinine concentration is sometimes used instead as a measure of renal function, but is only a rough guide.”<sup>2</sup>

The BNF does not make any recommendation on which nomogram should be used for correcting for age, weight and sex.

### New classification of CKD

Many countries, including the UK, have now adopted the K/DOQI classification of CKD (see Panel 2, p407). This classification has been endorsed by the National Service Framework (NSF) for Renal Services in England<sup>3</sup> and the recently published UK

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### Panel 1: Classification of renal impairment as stated in the BNF

Grade	Absolute glomerular filtration rate	Serum creatinine (approx)
Mild	20–50 ml/min	150–300 µmol/L
Moderate	10–20 ml/min	300–700 µmol/L
Severe	< 10ml/min	>700 µmol/L

guidelines for chronic kidney disease in adults.<sup>1</sup> The classification is based predominantly on estimated GFR (eGFR), although in the earlier stages of CKD (stages 1 and 2) other clinical evidence (eg, presence of proteinuria) is also important. All clinical biochemistry laboratories have now been advised by the Department of Health to report eGFR with each measurement of serum creatinine concentration, as part of the implementation strategy of the NSF for Renal Services. It is intended that the five-staged system will facilitate diagnosis, recognition and management of kidney disease.

### — Measuring renal function

Glomerular filtration rate (GFR) is a measure of the efficiency with which the kidneys remove waste products, such as creatinine and drugs, from the bloodstream. A normal GFR is 80–120ml/min.

For routine estimation of GFR, the use of prediction equations that adjust for differences in creatinine production rates have become well established. The two most common equations used in adults are the Cockcroft and Gault equation<sup>4</sup> and the newer 4-variable Modification of Diet in Renal Disease (MDRD) formula, endorsed by the UK CKD guidelines.

Serum creatinine itself is not an adequate measure of renal function because it is influenced by many factors. Creatinine is produced at a relatively constant rate for each individual, as a result of muscle

Panel 3: Other factors affecting serum creatinine concentration	
Factors affecting serum creatinine	Effect on serum creatinine concentration
Malnutrition, ageing, liver disease, muscle paralysis	Reduction
Eating meat (exogenous source of creatinine)	Increase
Exercise (increases rate of endogenous creatinine production)	Increase
Taking cimetidine, trimethoprim or salicylates (these drugs inhibit tubular secretion of creatinine)	Increase — most commonly noticed in advanced CKD
Taking corticosteroids, vitamin D metabolites or fibrates (these drugs modify production and release of creatinine)	Increase — most commonly noticed in advanced CKD
Ketoacidosis	Increase (due to interference in some assays for serum creatinine)

metabolism, and the rate of creatinine production is proportional to muscle mass. Creatinine production tends to be higher in people of African origin than in people of European or Asian origin.<sup>5</sup>

Creatinine is cleared from the circulation almost exclusively by glomerular filtration, although active tubular secretion by the proximal tubules can contribute significantly to overall creatinine clearance when GFR is markedly reduced. Serum creatinine concentration therefore depends on the balance between production rate (ie, muscle mass) and GFR. At any given level of GFR, serum

creatinine is higher in muscular patients and lower in patients with reduced muscle mass. Other factors may also have an effect on serum creatinine concentration, as outlined in Panel 3, thus distorting eGFR and creatinine clearance estimations.

**Cockcroft and Gault equation** The Cockcroft and Gault equation can be used to estimate creatinine clearance (CrCl), which is the amount of creatinine excreted in urine both due to glomerular filtration and active secretion from the proximal tubules of the kidney, as shown in the following formula:

$$\text{CrCl (ml/min)} =$$

$$\frac{F \times (140 - \text{age in years}) \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

Where F = 1.04 (female) and 1.23 (male)

The Cockcroft and Gault equation provides a creatinine clearance calculation which does not take body surface area (BSA) into account. Body weight is used in this formula as a marker of muscle mass. However, this leads to overestimation of muscle mass, and of creatinine clearance in obese patients and the opposite is true in underweight patients. Some authorities suggest using ideal body mass instead of actual body mass in individuals who are at extremes of body weight.

Furthermore, estimating CrCl from a serum creatinine level assumes that renal function is stable and that the serum creatinine level is relatively constant. With rapidly changing renal function, the serum creatinine levels will no longer reflect the true creatinine clearance rate.

**MDRD equation** The MDRD equation is derived from a regression analysis of a major study involving over one million adults.<sup>6</sup>

### Panel 2: Classification of chronic kidney disease<sup>4</sup>

Stage	Description
1	Normal glomerular filtration rate (GFR); GFR >90 ml/min/1.73m <sup>2</sup> with other evidence of chronic kidney damage*
2	Mild impairment; GFR 60–89 ml/min/1.73m <sup>2</sup> with other evidence of chronic kidney damage*
3	Moderate impairment; GFR 30–59 ml/min/1.73m <sup>2</sup>
4	Severe impairment: GFR 15–29 ml/min/1.73m <sup>2</sup>
5	Established renal failure (ERF): GFR <15 ml/min/1.73m <sup>2</sup> or on dialysis

\*The “other evidence of chronic kidney damage” may be one of the following:

- Persistent microalbuminuria
- Persistent proteinuria
- Persistent haematuria (after exclusion of other causes, eg, urological disease)
- Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, eg, polycystic kidney disease, reflux nephropathy
- Biopsy-proven chronic glomerulonephritis (most of these patients will have microalbuminuria or proteinuria, and/or haematuria)

Patients found to have a GFR of 60–89 ml/min/1.73 m<sup>2</sup> without one of these markers should not be considered to have chronic kidney disease and should not be subjected to further investigation unless there are additional reasons to do so.

The equation is shown in Panel 4. Following international acceptance of eGFR as the recommended measure, many virtual calculators have been made available, which can calculate eGFR using the patients' age, gender, racial origin and serum creatinine level.

The MDRD equation provides an estimate of GFR that is normalised to a standard BSA of 1.73m<sup>2</sup>, thus the reporting units for eGFR are ml/min/1.73m<sup>2</sup>. As a general rule, as body size increases so does kidney size and GFR; hence serum creatinine concentration remains constant despite increased creatinine production. Since renal size and metabolic rate correlate with BSA, the MDRD equation is currently the best proven approach to accurate mathematical estimation of renal function.

**Twenty-four hour urine collection** One other way of estimating GFR is via 24h urine collection. However, this method is inherently inaccurate by virtue of the technical difficulties of the collection process. It requires maximal patient co-operation and it can result in grossly abnormal estimates of GFR. This technique tends to overestimate the true GFR by an average of 15–30 per cent in stages 4 and 5, due to tubular secretion of creatinine.<sup>7</sup>

### Comparing the equations

The Cockcroft and Gault equation was originally validated against measured creatinine clearance as assessed by 24h urine collection, whereas the MDRD equation was validated against GFR measured as urinary clearance of the isotope <sup>125</sup>I-iothalamate. This estimate of GFR was normalised to body surface area ie, ml/min/1.73m<sup>2</sup>. Many groups have

### Panel 5: Comparison of estimates of kidney function for two patients with the same serum creatinine

Patient	Creatinine clearance using Cockcroft and Gault (ml/min)	eGFR using MDRD equation (ml/min/1.73m <sup>2</sup> )
Muscular, black male, age 20 years, weight 90kg. Serum creatinine 110µmol/L	120ml/min	>90ml/min/1.73m <sup>2</sup> (normal renal function)
Thin, caucasian female, age 75 years, weight 50kg. Serum creatinine 110µmol/L	29ml/min	40ml/min/1.73m <sup>2</sup> (stage 3 chronic kidney disease)

compared and contrasted the two equations.<sup>8</sup> Neither is perfect, particularly in patients with relatively normal kidney function, but the MDRD equation has achieved widespread acceptance internationally, and is endorsed by the UK CKD guidelines. A recent review looked at the evidence to support the use of the MDRD equation compared with the well established Cockcroft and Gault equation.<sup>9</sup> There is compelling evidence for the use of the MDRD equation in stages 3, 4 and 5 of CKD, where it provides a less biased, more precise and accurate prediction of GFR than estimates using the Cockcroft and Gault equation. However, some important limitations do apply when using the MDRD equation (see p409). The main advantage of the MDRD equation is that eGFR can be calculated without knowledge of body weight, unlike the Cockcroft and Gault equation.

It must be remembered that, since both these methods are based on serum creatinine

levels, they are only useful if the serum creatinine levels are stable and representative (see Panel 3, p407).

Widespread use of these prediction equations across the world has refocused attention on the variability between the different techniques used for measuring serum creatinine concentration. This variability can result in a marked diversity between laboratories in the number of people who would be diagnosed as having stage 3 CKD, for example. In the UK, work is under way to ensure that all laboratories use correction factors, depending on the type of creatinine assay they use, so that estimates of GFR will be comparable across the country.

### Drug dosing in CKD patients

Errors in prescribing for patients with renal impairment are common, and often cause harm.<sup>10</sup> Perhaps the most important type of error is failure to adjust the dose of renally cleared drugs relative to the degree of kidney dysfunction. These errors apply both to inpatient practice,<sup>10</sup> outpatient practice,<sup>11</sup> and prescribing in long-term care.<sup>12</sup> In addition, a recent review drew attention to the marked differences between the recommendations of four "definitive" information sources on adjustment of dose and dose interval depending on renal function.<sup>13</sup> However, there were some limitations in this review, as highlighted in subsequent correspondence in the *BMJ*.

Failure to adjust drug doses for patients with renal impairment is often related to the difficulty in recognising CKD, since most patients with this condition are largely asymptomatic. Introduction of the new CKD guidelines and national reporting of eGFR will improve recognition of CKD, and thus recognition of those patients who need their drug doses adjusting accordingly. Panel 5 shows the estimated kidney function of two patients with the same serum creatinine using the two most widely used predictive equations, Cockcroft and Gault and MDRD. The significance of the

### Panel 4: Estimation of glomerular filtration rate

Kidney function in patients with chronic kidney disease (CKD) should be assessed by formula-based estimation of glomerular filtration rate (GFR), preferably using the four-variable Modification of Diet in Renal Disease (MDRD) equation:

$$\text{GFR (ml/min/1.73m}^2\text{)} = 175 \times \{[\text{serum creatinine } (\mu\text{mol/L})/88.4]^{-1.154}\} \\ \times \{\text{age (years)}^{-0.203}\} \\ \times 0.742 \text{ if female and} \\ \times 1.21 \text{ if African American or African Caribbean}$$

Creatinine assays vary between laboratories. This version of the MDRD equation, using a constant of 175, replaces an earlier one using a constant of 186 and is designed for use with assay results that have been brought into line with the gold standard technique, isotope dilution mass spectrometry.

Until laboratories are able to report results in this way, there are two shortcuts which can be used:

- Prediction tables can be used to estimate GFR from serum creatinine, age, gender and ethnicity. Such tables can be found in appendix 1 of concise CKD guidelines (available at [www.renal.org/CKDguide](http://www.renal.org/CKDguide))
- An online eGFR calculator based on the MDRD equation, requiring input of the patient's age, gender, racial origin and serum creatinine (available at [www.renal.org/eGFRcalc/GFR.pl](http://www.renal.org/eGFRcalc/GFR.pl))

differences in estimates of kidney function arising from the two equations is paramount in drug dosing, especially at the extremes of body size.

One major concern with the adoption of the UK CKD guidelines and thus using the MDRD to calculate eGFR, is that eGFR is normalised to a standard BSA of 1.73m<sup>2</sup> and as such the reporting units are ml/min/1.73m<sup>2</sup>. When considering drug dose adjustment in practice, it is important that this estimate is corrected to the patient's actual GFR (ml/min). If a patient's BSA is <1.73m<sup>2</sup>, then their renal function is likely to be less than that reported as the eGFR, so the effect of adjusting drug doses to the normalised eGFR would be to give bigger doses than actually required. Conversely, if a patient's BSA is >1.73m<sup>2</sup>, then their renal function is likely to be higher than that reported as the eGFR, so the effect of adjusting drug doses to the normalised eGFR would be to give smaller doses than actually required. The conversion to actual, non-normalised GFR is achieved by multiplying the eGFR by the actual BSA and dividing by 1.73m<sup>2</sup> as follows:

Actual GFR =

$$\text{Normalised eGFR} \times \frac{\text{Actual BSA}}{1.73}$$

**Actual BSA** Various equations have been developed over the years to calculate actual BSA and they all give slightly different results. In clinical practice, one of the most often used BSA formula is that of Mosteller, published in 1987.<sup>11</sup>

$$m^2 = \sqrt{\frac{\text{Height (cm)} \times \text{weight (kg)}}{3600}}$$

$$m^2 = \sqrt{\frac{\text{Height (in)} \times \text{weight (lb)}}{3131}}$$

This relatively simple equation can be memorised and is easily calculated with a hand-held calculator. Alternatively, pre-formatted BSA calculator programmes are available on many internet sites (eg, <http://bnf.org>, [www.nephron.org](http://www.nephron.org)).

Nearly all published recommendations for dose reductions in patients with reduced renal function (including manufacturers' recommendations) are based on CrCl (ml/min) estimations, derived from the Cockcroft and Gault equation, rather than a normalised eGFR. In clinical practice we are already aware of instances where patients have been given inappropriate doses of drugs as a result of incorrect dosing based on eGFR, when the dosing advice was referring to CrCl.

We believe that estimates of renal function made using the Cockcroft and Gault equation, ie, non-normalised CrCl

(ml/min), should be used to adjust individual drug doses until such a time as the standard reference text dosing advice is changed to reflect dosing advice for normalised eGFR. Definitive guidance from the BNF and the Medicines and Healthcare products Regulatory Agency is urgently needed on this issue.

Where it is important to have a precise measure of GFR, for instance when using drugs that are renally cleared but have a narrow therapeutic index, it is preferable to measure GFR using an isotopic method rather than relying on a creatinine-based prediction formula (eg, <sup>51</sup>Cr ethylenediaminetetraacetic [EDTA] clearance). <sup>51</sup>Cr EDTA is cleared almost entirely by glomerular filtration, and measurement of its disappearance rate from the circulation or appearance in urine can be used to estimate GFR. However, it is important to note that isotopic GFRs are also commonly reported as normalised values (ie, ml/min/1.73m<sup>2</sup>) so the same caution should apply here when adjusting drug doses.

Avoidance of serious adverse drug events among patients with CKD therefore requires two components: a reliable system for detection of reduced GFR, and clear, consistent guidance on how drug dosage should be adjusted to GFR.

## Limitations

**Extremes of body weight** For most patients, the difference between the Cockcroft and Gault and MDRD equations is minor. However, both equations tend to produce an inaccurate estimate of renal function at extremes of body weight. Where an accurate GFR is deemed necessary, for example in chemotherapy dosing, then isotopic measurements should be performed.

**Ethnic groups** The Cockcroft and Gault equation was only validated in Caucasians. The MDRD equation was validated in Caucasians and African-Americans. Neither equation has been formally validated in patients of Asian origin, but preliminary results suggest that the MDRD formula remains valid in this patient group.

**Renal transplant recipients** In a recent study, Mariata *et al* compared Cockcroft and Gault estimates to MDRD estimates in renal transplant recipients.<sup>12</sup> Their study confirmed that MDRD gave a more accurate estimation of kidney function than Cockcroft and Gault, but was still not a good predictor of GFR when applied to transplant patients. However, Poggio *et al* concluded that in renal transplant recipients, including those treated with calcineurin inhibitors as part of their immunosuppressive regimen, the MDRD equation was superior to the Cockcroft and Gault equation.<sup>13</sup> That said, it is noteworthy that in

1992 the original Cockcroft and Gault formula was revalidated in renal transplant patients and was shown to correlate well in this patient group.<sup>14</sup>

## Patients with normal renal function

Neither the Cockcroft and Gault equation nor the MDRD equation give reliable estimates in people with normal or mildly reduced renal function. The MDRD equation can underestimate normal renal function by as much as 30 per cent when compared with gold standard methods (isotopic measurement of GFR).

Further research is required into finding more accurate methods of estimating GFR for these patient groups.

## Challenges

Avoidance of serious adverse drug events in patients with CKD requires a reliable system for detection of reduced GFR. Following publication of the NSF for renal services and the UK CKD guidelines, many clinical biochemistry laboratories will be reporting eGFR in addition to serum creatinine. This process will facilitate early identification of patients with impaired renal function. Online eGFR calculators can be easily used to obtain an eGFR value. These numbers essentially translate into "percentage of normal kidney function" because a normal GFR is approximately 100ml/min/1.73m<sup>2</sup>.

Clear, consistent guidance on how drug dosage should be adjusted to GFR, and careful choice and use of drugs is also required. The Renal Drug Handbook is a practical reference guide which seeks to assist health care professionals in this process.<sup>15</sup>

Standard drug reference texts (the BNF, summaries of product characteristics, The Renal Drug Handbook, etc) all make recommendations for dose adjustment in renal impairment based either on measured CrCl (using 24h urine creatinine clearance) or on estimated CrCl (using the Cockcroft and Gault formula). It is likely to be some time before the dose recommendations in these texts reflect the five-stage classification of CKD according to GFR normalised for body size. In the interim, we believe that, in practice, the MDRD equation will be used to classify a patient's degree of renal impairment according to the UK CKD guidelines. However, for individual drug dosing and estimation of CrCl in practice, the Cockcroft and Gault estimate will remain the mainstay until the standard texts reflect the change in guidance to eGFR.

Before an eGFR normalised value is used for drug dosing it should be converted to actual, non-normalised GFR using a patient's actual body surface area (BSA), as described earlier. This is especially relevant for patients with CKD stages 3–5 and at extremes of body size.

When prescribing for patients with CKD a number of iatrogenic problems can arise. These may be due to:

- Inability to excrete a drug or its metabolites, resulting in drug toxicity
- Some drugs no longer being effective when renal function is reduced
- Increased sensitivity to some drugs and/or their side effects
- Altered pharmacokinetics/pharmacodynamics
- Side effects being tolerated poorly by patients in ERF
- Multiple drug therapies
- Specific patient factors (eg, intercurrent illness, dehydration)

Most patients with early CKD do not progress to established renal failure, but CKD is associated with a greatly increased risk of morbidity and mortality due to cardiovascular disease. The pharmacist has a role to play in methodical prescription assessment and appropriate medicine dose review for all patients with CKD. Optimal management of the risk factors for cardiovascular disease has been shown to reduce the risk of progression from early CKD to ERF. Pharmacists will have a role in identifying these patients in the community, advising on disease modifying or prevention strategies such as statins, antihypertensives, aspirin, smoking cessation and ensuring medication compliance, as well as in giving advice to patients and prescribers on drug dose adjustment in CKD.

## Conclusions

Many of the problems associated with failure to adjust drug doses in the presence of renal impairment relate to the difficulty in recognising the presence of CKD. Most patients with CKD are asymptomatic and, as the population ages, more patients are going to develop the disease. It is hoped that with adoption of the new UK CKD guidelines and eGFR reporting, more of these patients will be identified. These patients will tend to require more medicines, many of which are potentially toxic to the kidney or can cause damage to other organs in overdose. Hence accurate estimation of GFR is an essential consideration when prescribing drug therapy for this patient group. With appropriate dose adjustment many patients will avoid the unnecessary morbidity associated with inappropriate prescribing in CKD.

### Guideline summary

A shorter article describing the new chronic kidney disease classification, by the same authors, entitled "How the reclassification of kidney disease impacts on dosing adjustments", was published in the 30 September issue of *The Pharmaceutical Journal*. It can be accessed at [www.pjonline.com](http://www.pjonline.com)

However, the authors are already aware of a number of such incidents having occurred due to confusion between eGFR and CrCl. The UK Renal Pharmacy Group has opened discussions with the National Patient Safety Agency to seek further advice, and an appropriate process to warn other health care professionals. In addition, the authors are also in discussion with the BNF to ask for its assistance in highlighting the change in definition of CKD and the concomitant potential for confusion with drug dosing in renal impairment.

When calculating renal function, MDRD eGFR normalised estimates largely correlate with Cockcroft and Gault estimates for CKD stages 3–5. However, the gold standard for dosage adjustment in CKD remains the Cockcroft and Gault equation, until such a time as the reference texts recommend doses based on GFR normalised for body size. Both equations have limitations at extremes of body weight which need to be adjusted for. The National Electronic Library for Medicine published a recent in-focus review on eGFR earlier this year.<sup>16</sup> Independently it has drawn similar conclusions.

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### Comment from the BNF

The authors draw a valuable distinction between different expressions of renal function.

The BNF categorisation of renal impairment, focussing on drug elimination rather than on grading chronic kidney disease, is intended to be used in conjunction with advice given on drug dose adjustments. Following discussions with Charlie Tomson, Appendix 3 of BNF 52 (September 2006) warns that the eGFR cannot be used to work out doses in renal impairment because dose adjustment advice is almost always based on creatinine clearance values. An alternative but less satisfactory substitute for creatinine clearance is the individual's actual GFR calculated from the equation in this article, which is now also in BNF Appendix 3.

It is likely that we will have to wait a long time before dose adjustment figures are reliably and consistently expressed in terms of eGFR. Ideally, pharmacokinetic studies are required that rely on classification of renal function according to the MDRD formula. In the meantime, calculating the dose for those with impaired renal function calls for even greater vigilance. — *Dinesh Mehta, executive editor*

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