How the reclassification of kidney disease impacts on dosing adjustments

In this article, Andrea Devaney, Caroline Ashley and Charlie Tomson highlight potential problems introduced by the changes to how renal impairment is classified and explain why extra care is needed when working with the new terms.

In 2003 the UK adopted the US Kidney Disease Quality Outcomes Initiative (K/DOQI). This led to a change in the terms used to describe renal impairment. For example, "end stage renal failure" was replaced by "established renal failure" (ERF). There was also a shift from describing the degree of renal impairment as mild, moderate or severe. Instead, the new chronic kidney disease (CKD) guidelines define the degree of renal function in five stages, with stage 1 indicating near normal renal function and stage 5 indicating ERF or that dialysis is required.

In addition, the CKD guidelines define the measure of renal function as a glomerular filtration rate (GFR), which has been normalised to a body surface area of 1.73m² (the normal mean value for adults) and are presented in Panel 1.

### Estimating and using GFR

GFR is a measure of the efficiency with which the kidneys can remove waste products, such as creatinine, and drugs from the bloodstream. A normal GFR is 80–120ml/min. To estimate GFR, a number of different methods can be used. Many pharmacists and other health professionals involved with drug dosing in renal impairment will use a prediction formula. Historically, the most well-established formula is that of Cockcroft and Gault, which calculates creatinine clearance (CrCl) in ml/min. This is a surrogate marker for GFR:

\[
\text{CrCl} (\text{ml/min}) = \frac{F \times [140 - \text{age}] \times \text{weight (kg)}}{\text{serum creatinine (µmol/L)}}
\]

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

This equation is by no means a perfect marker of renal function. Creatinine is cleared from the circulation almost exclusively by glomerular filtration, but when renal function

*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, proteinuria or haematuria, or a combination)

Patients found to have a GFR of 60–89ml/min/1.73m² without one of these markers should not be considered to have CKD and should not be subjected to further investigation unless there are additional reasons to do so.

### Panel 1: Classification of chronic kidney disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Normal GFR (GFR &gt; 90ml/min/1.73m² with other evidence of chronic kidney damage)*</td>
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<tr>
<td>2</td>
<td>Mild impairment (GFR 60–89ml/min/1.73m² with other evidence of chronic kidney damage)*</td>
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<tr>
<td>3</td>
<td>Moderate impairment (GFR 30–59ml/min/1.73m²)</td>
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<tr>
<td>4</td>
<td>Severe impairment (GFR 15–29ml/min/1.73m²)</td>
</tr>
<tr>
<td>5</td>
<td>Established renal failure (GFR &lt; 15ml/min/1.73m² or patient on dialysis)</td>
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It may be beneficial to ensure that colleagues careful choice and use of drugs is required. Pharmacists should make sure they know MDRD eGFR estimates (ml/min/1.73m²) are introduced. This is called the modification of the National Service Framework for Renal Services and Department of Health advice, which formula their biochemistry laboratory uses and confirm the reference units used. If the laboratory reports an eGFR, this must be adjusted to take account of the patient’s body surface area before amending any drug dosages relative to his or her degree of renal impairment. It may be beneficial to ensure that colleagues are aware of the differences between the two estimates and the potential problems that may arise with their incorrect use. Careful choice and use of drugs is required when prescribing for individuals with any renal impairment. The Renal Drug Handbook is a practical guide which seeks to assist health care professionals in this process. In line with the implementation strategy of the National Service Framework for Renal Services and Department of Health advice, most chemical pathology laboratories are now reporting the eGFR value in parallel with serum creatinine values. This is an excellent development because it will speed up the detection of CKD and encourage timely and appropriate referral to renal specialists. Previously, laboratories only reported serum creatinine levels and this could hinder accurate diagnosis. It should, however, be noted that MDRD eGFR estimates are not the same as Cockcroft and Gault estimates of CrCl, although the two estimates are largely similar for CKD stages 3 to 5. The belief is that eGFR reporting will improve the overall care of patients with renal impairment. However, it is imperative that all pharmacists are aware of these changes and that drug dosing is not based on eGFR values because it is the individual’s actual, non-normalised GFR that determines how quickly any drug will be cleared by his or her kidneys. In contrast, the eGFR tells us what that an individual’s kidneys would be capable of clearing if he or she had a body surface area of 1.73m². For patients with a body surface area >1.73m², using an MDRD eGFR can result in underestimation of the patients renal function with resultant under dosing. The best estimate of an individual’s actual, non-normalised GFR remains the Cockcroft and Gault CrCl. Alternatively, an eGFR value can be easily converted to an actual GFR value by multiplying the eGFR by the patient’s body surface area and dividing by 1.73m² as follows:

Actual GFR = eGFR \times \text{Actual body surface area} \div 1.73

Clearly, the adoption of the new classification of kidney disease has presented the potential for confusion between GFR and eGFR, which could give rise to fatal errors. Panel 2 lists some summary points and our recommendations in order to minimise risks.

**Conclusion**

The introduction and use of the MDRD formula and eGFR in practice will aid the earlier detection and appropriate referral of patients with CKD. However, in our opinion, an eGFR should not be used to adjust drug doses. We believe Cockcroft and Gault should remain the gold standard to estimate GFR when adjusting drug doses to an individual’s renal function. The delayed uptake of the new classification of renal disease is, in itself, a potential source of confusion. Most doses quoted in standard reference sources are based on Cockcroft and Gault and these should be used until such a time as the standard reference texts are changed to reflect drug dosing advice for normalised eGFR. The National Electronic Library for Medicine has published a recent in-focus review on eGFR, in which it independently, draws similar conclusions.

Another example is that the current British National Formulary is still using the terms mild, moderate and severe to describe renal disease. We have been in discussion with the BNF to ask for their assistance in highlighting the change in definition of CKD and the concomitant potential for confusion with drug dosing in renal impairment. These discussions are ongoing. Clearly, iatrogenic harm can result from inappropriate drug dosing. The authors of this article 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 National Patient Safety Agency to seek clarification advice, and an appropriate process to warn other health care professionals.

### Panel 2: Summary points and practice recommendations

- MDRD eGFR estimates (ml/min/1.73m²) are not the same as Cockcroft and Gault estimates of CrCl (ml/min).
- When estimating renal function for patients at both extremes of the weight spectrum neither equation is perfect.
- Pharmacists should make sure they know which formula their biochemistry laboratory uses and confirm the reference units used.
- If the laboratory reports an eGFR, this must be adjusted to take account of the individual’s body surface area before amending any drug dosages relative to his or her degree of renal impairment.
- It may be beneficial to ensure that colleagues are aware of the differences between the two estimates and the potential problems that may arise with their incorrect use.
- Careful choice and use of drugs is required when prescribing for individuals with any renal impairment.

### References


### Comment from the BNF

The authors draw a valuable distinction between different expressions of renal function. Following discussions with Charlie Tomson, Appendix 3 of BNF 52 now 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 the 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. In the meantime, figuring out the dose for those with impaired renal function calls for even greater vigilance. — Dinesh Mehta, executive editor