

dose will need to be adjusted in patients with renal impairment.

There are two ways of doing this:-

- Increase the dosing interval, whilst the dose remains unchanged, or
- Decrease the dose, whilst the dosing interval remains unchanged
- For some drugs, e.g. aminoglycosides, it is necessary to both reduce the dose and increase the dosing interval.
- The objective is to produce a plasma drug profile which approaches that normally achieved in the absence of renal failure.

Effective GFRs on Dialysis

Renal Replacement Technique	Principle of Removal	Typical Effective GFR Achieved (mL/min)
PD	Dialysis and Ultrafiltration	5-10
Intermittent HD / HDF	Dialysis and Ultrafiltration	250-300 during dialysis < 10 off dialysis
CAVH / CVVH	Ultrafiltration	15-30
CAVHD/CVVHD	Dialysis and Ultrafiltration	25-35

Supplementary doses for RRT

Some texts quote supplementary doses to be given after intermittent HD/HDF. They will only be important for drugs with a low Vd and a narrow therapeutic range which are cleared efficiently by dialysis.

In practice, it is better to adjust the timings of doses so that the next dose falls after the RRT session rather than add in extra doses.

With CVVH/CVVHD, the dialysis process is continuous, so supplementary doses are not necessary. The patient may be dosed at any time of day as dictated by the treatment protocol.

Sources of Dosing Information

- Renal Drug Handbook 5th Edition 2018
Dunleavy A, Ashley C,
- Renal Drug Database
<https://renaldrugdatabase.com/>
- Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children 5th Edition 2007. Brier ME, Aronoff GR
<http://www.kdp-baptist.louisville.edu/renalbook/>

Reminder

Dialysis patients

Don't try to calculate the patient's renal function. Being on dialysis, by definition they have end stage renal disease so have no renal function. Fluctuations in serum creatinine are due to the bloods being taken either pre- or post- dialysis. Dose as in CrCl<10ml/min

Transplant patients

Don't assume a transplant patient has normal renal function – a few do but most don't. Calculate renal function as usual and then amend drug doses accordingly.

AKI patients

MDRD and C&G equations are not very accurate with rapidly changing serum creatinine. They can be used but keep re-checking the patient's renal function daily.

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Drug Dosing in Renal Impairment & Dialysis



Many drugs or their metabolites are eliminated from the body via the kidneys. In renal impairment, these drugs will tend to accumulate leading to toxicity.

Dialysis will replace some of the excretory functions of the kidneys, but is still not equivalent to fully functioning kidneys.

Hence it is necessary to amend doses of renally excreted drugs according to the patient's degree of renal impairment, or the type of dialysis they are undergoing.

In order to do this, it is necessary to calculate the patient's creatinine clearance (CrCl), or their estimated glomerular filtration rate (eGFR).

www.renalpharmacy.org.uk

Cockcroft & Gault Equation

$$\text{CrCl} = \frac{[140 - \text{Age (years)}] \times \text{Weight (kg)}}{\text{Plasma creatinine } (\mu\text{mol/L})}$$

- For males, multiply above equation by 1.23
- For females, multiply above equation by 1.04
- Use ideal body weight in obesity (i.e. If patient's weight is > 15% over IBW)

The equation is not accurate if:-

- patient is < 15 years or > 90 years of age
- patient has rapidly changing renal function (ie. creatinine varying by > 40 $\mu\text{mol/L}$ per day).
- patient has a serum creatinine > 350 $\mu\text{mol/L}$
- patient is pregnant
- patient is an amputee
- patient is severely malnourished

Cockcroft and Gault is the preferred method for estimating renal function or calculating drug doses in patients with renal impairment who are elderly or at extremes of muscle mass; it provides an estimate of CrCl (which is not equivalent to eGFR).

MDRD Equation

$$\begin{aligned} \text{eGFR (mL/min/1.73m}^2\text{)} = & 170 \times (\text{serum creatinine})^{-0.999} \\ & \times (\text{age})^{-0.176} \\ & \times (0.762 \text{ if female}) \\ & \times (1.180 \text{ if African American}) \\ & \times [\text{Serum Urea Nitrogen}]^{-0.170} \\ & \times [\text{Alb}]^{+0.318} \end{aligned}$$

It is less accurate than the CKD-EPI formula when eGFR is greater than 60 mL/min/1.73m². It also overestimates GFR in elderly patients.

In patients at both extremes of muscle mass, eGFR should be interpreted with caution. Reduced muscle mass will lead to overestimation of GFR and increased muscle mass will lead to

underestimation of the GFR.

The calculated eGFR is a normalised value, hence it may be necessary to correct for the patient's actual surface area.

A calculator for eGFR may be found at:- www.nephron.com/mdrd/default.html

CKD-EPI Formula

- Estimates GFR from serum creatinine, age, sex, and race.
- More accurate than the MDRD Study equation, particularly in people with higher levels of GFR.
- It is the recommended method for estimating GFR and calculating drug doses in most patients with renal impairment, but is not routinely used in many UK labs yet.

High Risk Drugs

- ❖ Drugs normally excreted via the kidneys
- ❖ Drugs with a narrow therapeutic index, e.g. digoxin
- ❖ Drugs metabolised by the liver but with pharmacologically active metabolites that are excreted via the kidneys e.g. morphine
- ❖ Drugs known to be nephrotoxic e.g. NSAIDs, methotrexate, chemotherapy

Drug Accumulation

- ❖ It should be noted that drug accumulation does not always lead to renal impairment
- ❖ The end organ damage is what is effectively seen if a patient overdoses on that drug
- Some cephalosporins, penicillins, carbapenems \Rightarrow grand mal fits
- Opiates \Rightarrow respiratory depression & sedation
- Aminoglycosides \Rightarrow nephrotoxicity & ototoxicity
- Allopurinol \Rightarrow bone marrow suppression

Drug Dosing

- If non-renal clearance accounts for elimination of more than 50% of a drug, then no adjustments need be made to dose or frequency of administration.
- Dosages of toxic drugs which are mainly excreted in active form by the kidney (i.e. as unchanged drug or active metabolites) may need to be modified to avoid accumulation.
- If the drug is unaffected by renal impairment, it may be used in usual doses and the patients should be monitored for signs of increased sensitivity to the effects of the drug or to the side effects.
- Drugs that require therapeutic levels quickly may require a loading dose as the time taken to reach steady state will be prolonged for drugs where the metabolism and excretion is slowed in renal impairment.
- If dose amendment is required, then dose, dose interval or both can be adjusted to achieve the desired therapeutic effect. For example, with antibiotics, particular peak concentrations are required for optimal bactericidal or bacteriostatic effects, so typically the normal dose given less frequently is prescribed. Conversely, with digoxin, a steady plasma concentration is desirable, so the dosing interval remains at 24 h, and the dose is reduced.
- ❖ **Loading Dose**
Generally unchanged. If a drug is excreted via the kidneys, in renal impairment the half life will be increased, so it will take longer to reach steady state. For drugs such as antibiotics, a loading dose will enable therapeutic drug levels to be attained quickly.
- ❖ **Maintenance Dose**
As a general rule, if a drug is normally excreted via the kidneys, its maintenance